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2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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Euthymia: why it really does matter

Few would argue against the value of a life of positive emotions, meaning and purpose, competence, achievements, and quality relationships with others. Such a life is obviously worth living and worth striving for. A reasonable question to ask, though, is whether directly promoting such a life falls under the provenance of psychiatry and other mental health professions. The alternative view is that mental health services should focus on treating disorders that act as obstacles getting in the way of such a life being realized, rather than promoting it directly. Fava and Guidi[1], in this issue of the journal, argue for the former view, organizing their approach around the central concept of euthymia. I would like to endorse their stance and elaborate on some reasons why.

First, some mental health problems might benefit from being conceptualized as having essential components of low well-being. For example, suicidal thinking has often been talked about as a negative view of the future, but recent attempters high in suicide ideation consistently show a lack of anticipated positive personal events in their future, without showing an excess of future negative thoughts[2]. Furthermore, self-reported hopelessness correlates with lack of positive future thoughts, and shows no significant correlation with negative future thoughts[3].

In other words, those who are suicidal specifically suffer from the absence of a component of a good life – looking forward to positive things in the future, both in the short and long term. The understanding of suicidal thinking could, therefore, be enhanced by a greater focus on the positive well-being component of future-thinking, normally present but absent when people feel suicidal.

It is not that traditional approaches do not appreciate this kind of point at all – anhedonia is a good example, where the absence of a pleasure response is recognized as central to depression – but there is enormous scope for further work exploring how the understanding of different psychiatric conditions can be enhanced by the application of well-being frameworks.

Second, it is a disappointing but well established fact that some mental disorders, even when responsive to initial treatment, prove to be relapsing or recurring. Fava and Guidi point to the example of depression, where 50% of those successfully treated after a first episode experience at least one further episode, with the risk increasing further after subsequent episodes[4].

What is the role of a well-being approach here? Consider the following analogy. A young girl is playing in a park but does not notice a large hole; she falls down the hole and cannot get herself out; her father hears her cries and comes and pulls her out. After soothing her, does her father go off to what he was doing before and leave the child to play at the edge of the hole? Of course he does not. He takes her to a part of the park far away from the hole, where she will not fall in again. By getting people to a reduced level of symptoms or distress that takes them out of "the hole" and then leaving them there, we are doing the equivalent of leaving the child to play by the hole after rescuing her.

If we do not want people to relapse, we need to find ways to get them as far away from the hole as possible, and it is not necessarily safe to assume that they will be able to do that by themselves. It is here that more well-being focused approaches can come into their own, by both reducing residual symptoms and building well-being resources[5]. Given that residual symptoms are one of the strongest predictors of relapse[4], approaches such as well-being therapy[6] that target those symptoms would seem to be particularly valuable.

Third, many mental health problems are unfortunately long lasting or even chronic, whether in full or in a reduced form. Symptoms may not respond well to traditional treatment approaches, or residual symptoms may persist to a significant degree. Recovery-oriented practices[7] are based on the idea that personal recovery can occur even in the absence of clinical recovery.

The use of the term "recovery" in this personal context is somewhat confusing, referring as it does to people being able to live satisfying and meaningful lives even in the ongoing presence of illness symptoms. Once again, traditional approaches do recognize the value of not simply focusing on symptoms. However, it is fair to say that recovery-focused approaches do not seem well connected to the extensive psychological well-being literature that might inform them.

There is great scope for marrying mainstream well-being models with service provision for mental health problems. This could help in providing a fuller framework within which to understand the goals of those continuing to suffer the effects of mental health problems, and also to help them to think of how to attain those goals, using a structured approach such as well-being therapy. It is here that Fava and Guidi, in drawing on the model of Ryff[8] from the mainstream psychological literature, provide an excellent example of how such a marriage can work.

The discussion on relapse/recurrence and chronicity highlights an interesting area that requires further clarification. Recovery-based approaches have an underlying assumption that well-being is at least partially independent of illness/distress, such that a life of well-being can be fostered even as someone continues to be symptomatic. This is different from the relapse prevention discussion of moving a person further away from disorder by enhancing his/her well-being. The relapse discussion and the analogy of the hole in the park is based on the simpler idea of a single underlying dimension, with well-being at one end and illness/distress at the other, one in which they are incompatible with each other because they are opposites.

There is some debate about which of these approaches best fits the data[9], and it is likely the case that both views have some merit. A full understanding of this issue is yet to be reached. One way that this understanding will be progressed is by talking about specifics rather than broad classes. In some cases, the relationship will be more like a single dimension: for example, having a life full of positive emotions and being depressed seem incompatible and more like two ends of a single dimension. In

other cases a two-dimensional framework will fit better: someone could hear voices but also live a life that is purposeful and meaningful. In other words, it depends on which aspects of illness and which aspects of well-being are being talked about.

However, the important point for the discussion here is that, whether within a single- or a two-dimensional framework, there is value in promoting euthymia. Much work remains to be done on all of these issues, but there is exciting potential for advances in assessment and intervention in this area.

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Economics and mental health: the current scenario

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Economics and mental health are intertwined. Apart from the accumulating evidence of the huge economic impacts of mental ill-health, and the growing recognition of the effects that economic circumstances can exert on mental health, governments and other budget-holders are putting increasing emphasis on economic data to support their decisions. Here we consider how economic evaluation (including cost-effectiveness analysis, cost-utility analysis and related techniques) can contribute evidence to inform the development of mental health policy strategies, and to identify some consequences at the treatment or care level that are of relevance to service providers and funding bodies. We provide an update and reflection on economic evidence relating to mental health using a lifespan perspective, analyzing costs and outcomes to shed light on a range of pressing issues. The past 30 years have witnessed a rapid growth in mental health economics, but major knowledge gaps remain. Across the lifespan, clearer evidence exists in the areas of perinatal depression identification-plus-treatment; risk-reduction of mental health problems in childhood and adolescence; scaling up treatment, particularly psychotherapy, for depression; community-based early intervention and employment support for psychosis; and cognitive stimulation and multicomponent carer interventions for dementia. From this discussion, we pull out the main challenges that are faced when trying to take evidence from research and translating it into policy or practice recommendations, and from there to actual implementation in terms of better treatment and care.

Key words: Economic evaluation, cost-effectiveness, cost-benefit, cost-utility, return on investment, mental health policy, depression, psychosis, dementia

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Mental health economics has developed rapidly over recent decades. From an earlier "age of innocence", with apparently little recognition of resource scarcity by the research community, to a phase of "unbridled criticism", which rejected economics as having any legitimate role to play in evaluating treatment and care, the field has moved on noticeably[1].

There was perhaps an era of "undiscriminating utilization", characterized by methodological imprecision, poor quality data and over-hasty generalizations, but progress has now been made (in some countries at least) towards a more constructive development of questions and more robust answers. In terms of numbers, the cumulative total of reports on economic evaluation of mental health care and treatment has grown from approximately 100 in 1999 to over 4,000 in 2019.

Changes in mental health economics are far greater than suggested simply by these numbers. Developments are shown, for example, by research focus and journal interest moving beyond the mere parading of cost-of-illness (COI) numbers to a more discerning discussion of findings from cost-effectiveness and other economic evaluations. There are also wider demands for economics, motivated not only by commercial interests (e.g., of pharmaceutical companies) or cost-saving imperatives (e.g., of governments), but also by the need to inform a wide range of strategic, clinical, preventive, purchasing and person-centred decisions. Better data are available to feed into economic evaluations and associated investigations, including from birth cohorts, more ambitious epidemiological surveys, clinical trials with embedded economic components, and from provider or purchaser administrative records.

There are also better evaluative methods. The best-selling book on health economic evaluation has gone through four editions since 1987, more than doubling in size, and capturing the many developments in this area of study[2]. As well as improved empirical techniques, health economic evaluators are showing greater readiness to explore inequalities[3]. Another notable development has been inclusion of different outcomes, such as for dyads and family members and hedonic well-being, as well as more critical interrogation of the validity of quality adjusted life year (QALY) measures. Most importantly, recent years have seen the findings from economic evaluations having greater impacts, and there are now burgeoning opportunities for applying economic evidence to promote mental health policy or practice change in many countries.

These developments warrant a review and reflection on mental health economics. Despite encouraging progress, large evidence gaps still exist regarding the economic case for many areas of mental health treatment and care, with evidence also unevenly distributed globally and transferred sluggishly across health care, social care, and other implicated systems. In this paper, we provide an overview of current knowledge in mental health economics, describe evidence gaps and recent research trends, recommend areas for further research, and set out recommendations for policy and practice.

Economics and mental health are intertwined in multiple ways. We begin by discussing why economics is relevant in mental health, and setting out the main types of economic evaluation appropriate for interventions and their implications. Evidence is arranged according to mental health needs by points on the life course and diagnostic categories of mental, behavioural or neurodevelopmental disorders. This reflects the structure of how most such evidence is currently available and organized, and in using this approach we do not necessarily imply validity of diagnostic categories, as this topic is beyond the scope of this review. We offer a succinct rather than comprehensive summary of

this knowledge base, drawing out a range of issues and identifying both challenges and potential solutions at methodological, policy and practice levels. Throughout, readers will be directed to further readings and recent review papers for specific topics.

Despite rapid growth in cost-effectiveness and related studies in recent years, some areas nevertheless remain unexplored. We conclude by mentioning some of these gaps, and with a wider discussion of the main challenges that often emerge when attempting to move from empirical economic evidence to recommendations for strategic policy and for clinical action. We also set out a few possible responses to these challenges.

WHY ECONOMICS IS RELEVANT

Economics concerns the production, distribution and consumption of goods and services. Its relationship with mental health is bi-directional and complex.

On the one hand, the huge impact of mental ill-health on economics – through its deleterious consequences, such as productivity losses and heavier use of resources for treatment – is increasingly recognized with the help of disease-burden and COI studies. The latter aggregate the direct and indirect costs generated by a condition. These personal and economic consequences could affect the entire life course, and spillover into family and wider community impacts[4]. In 2011, the World Economic Forum projected that, by 2030, mental ill-health will account for more than half of the global economic burden attributable to non-communicable diseases, at US$6 trillion[5].

On the other hand, economic disadvantage is associated with a greater likelihood of mental illness, possibly through greater exposure to risk factors (e.g., social exclusion) and poorer access to protective factors (e.g., education), or a complex downward spiral (e.g., entanglement of poverty, treatment costs, employment difficulty; the so-called "drift" hypothesis)[6,7]. The European Psychiatric Association recently issued guidance on mental health and economic crises in Europe[8], based on a review of 350 articles, highlighting the need for policy approaches to tackle the complex, sizeable impacts.

Given that resources are scarce, and with an aim to maximize health and well-being, economic analyses are needed alongside effectiveness evidence for decision-makers to identify the best options in deploying available resources[7]. In some high-income countries, economic evaluation is now an almost obligatory component of any evaluation in health services research[4]. In the UK, for example, health technology appraisal mechanisms require formal cost-effectiveness evaluation to inform reimbursement and coverage, and to develop clinical guidelines such as those issued by the National Institute for Health and Care Excellence (NICE)[4].

Economic analyses commonly used in mental health intervention studies include cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). They differ one from another in terms of outcome measures (see Table 1).

CEAs focus on clinical or similar indicators such as specific symptoms or disabilities. Results from CEAs can help decision-makers by providing information on the additional cost of achieving an incremental improvement in an outcome measure (using a so-called incremental cost-effectiveness ratio, ICER). Unless there is clear evidence that an intervention improves outcome and simultaneously reduces cost, however, decisions essentially boil down to empirically-informed value judgements that cannot be solely addressed with economic evidence (or clinical evidence, for that matter).

Results from CUAs, usually expressed in cost per QALY gained, could be used to support such value judgments, with some countries having an agreed QALY threshold (e.g., £20,000 per QALY

Table 1 Main types of health economic evaluation

	Outcome measures	Comments
Cost-minimization analysis	None – Outcomes are assumed equivalent across interventions.	Limited use unless outcome evidence is convincing.
Cost-effectiveness analysis (CEA)	A single ("primary") outcome measured in "natural" units, such as symptoms *or* independence.	Limited by focus on a single outcome, but any recommendations from the study will be unambiguous.
Cost-consequences analysis (CCA)	Multiple outcomes measured in "natural" units, such as symptoms *and* independence *and* health-related quality of life.	Can capture all outcomes. Recommendation not always straightforward because outcomes might point in different directions.
Cost-utility analysis (CUA)	Generic, utility-based measure such as QALYs. Studies using DALYs are similar.	Findings can be used for strategic decision-making in the health sector. QALY or DALY measures might be too generic, and so miss the nuances of intervention effects in the mental health field.
Cost-benefit analysis (CBA)	Monetary values of outcomes, plus any savings in budgets.	Findings can be used for strategic decision-making across all policy sectors, but very difficult to monetize mental health outcomes.
Well-being economic evaluation	Subjective (probably hedonic) well-being.	Findings can be used for strategic decision-making across all policy sectors, but generic indicator (well-being) might miss nuances of intervention effects.

QALYs – quality adjusted life years, DALYs – disability adjusted life years

in the UK[9], and US$50,000 per QALY in the US[10]), although not without controversy. The QALY is an example of a generic outcome measure intended to be relevant across different disorders, and so to support more strategic decision-making within the health system, for example when allocating budgets between clinical specialties or making strategic decisions about priorities within a national health care system. By their very nature, generic measures such as QALYs – or disability adjusted life years (DALYs), which are more commonly used in low- and middle-income country (LMIC) contexts – cannot capture all of the subtleties of an individual condition or its treatment, and so are most usefully employed alongside rather instead of effectiveness measures in economic studies.

CBA requires outcomes to be valued in monetary terms. From a societal and public mental health perspective, it provides results expressed in net benefits (change in the monetary value of effects minus change in costs). CBAs are inherently difficult to do in mental health contexts, since there is no easy way to calculate what a reduction in symptoms or an improvement in independence would be worth in dollars, euros or other currencies.

Return on investment (ROI) analysis has recently being recommended by the World Health Organization (WHO) and the United Nations Development Program (UNDP) for making an investment case for mental health[11]. Many but not all of the "best practice" interventions had previously been subjected to WHO CHOICE (CHOosing Interventions that are Cost-Effective) analysis. ROI is a broad term that covers different types of analysis. The Methodological Guidance Note for this WHO/UNDP approach chooses to recommend a form of CBA: the monetary values attached to mental health outcomes could be seen as somewhat crude, but help to locate discussion of resource allocation to address mental illness in a broader economy-wide context.

Examples of these types of economic evaluations will appear throughout this paper, although we mainly discuss cost-effectiveness and cost-utility studies.

BEYOND DISEASE BURDEN

Evidence on the societal economic burden of mental health issues is instrumental in gaining the attention of policy-makers (especially those in non-health domains), by calculating the scale of the "problem", and in highlighting the mismatch between mental health burden and resource allocation.

Recent analyses using COI and value of statistical life (VSL, valuation based on willingness-to-pay to avoid certain risks) approaches have suggested a global cost of mental, neurological and substance use (MNS) disorders of US$2.5 trillion and US$8.5 trillion in 2010, respectively. Using the value of lost output or economic growth approach, which takes into account DALYs, the cumulative global economic impact of MNS was estimated at US$16.3 trillion between 2011 and 2030[5]. This huge economic impact exceeds cardiovascular disease, chronic respiratory disease, cancer and diabetes in its contribution to global burden of disease.

The current estimate of global median expenditure on mental health, however, is only US$2.5 per person annually (ranging from US$0.1 to US$21.7 across WHO regions), accounting for less than 2% of government health expenditure globally[12]. This low expenditure is a major reason for the wide gap between mental health needs and provision of intervention[4].

The gap is particularly wide in LMICs. In a recent analysis of data from 30 countries in the WHO Region of the Americas, for example, a ratio between mental health burden and expenditure ranging from 3:1 to 435:1 was reported[13], which was correlated with gross domestic product (GDP) after adjusting for purchasing power parity, with lower-income countries particularly affected by the imbalance.

There are a few successful examples in which these types of evidence on disease burden and COI have been used to raise public awareness and to lobby policy-makers in prioritizing resources to advance mental health care. For example, estimates of the global economic impact of dementia[14] were pivotal in recognition of the problem as a public health priority in 2012[15], and the subsequent G8 Dementia Summit, government policy briefs[16], and the creation of the World Dementia Council in 2013.

From a decision-maker perspective, however, evidence on disease burden and costs alone has limited use. It can certainly raise awareness of overall impact, but it does not offer recommendations of what needs to be done in response, whether in terms of treatments, care services, prevention and so on. Decisions need to be based on affordability, for example (requiring budget impact studies or cost-offset studies) and "value-for-money" information to guide public spending (requiring economic evaluation studies that consider both cost and outcomes).

Full economic evaluation, in this sense, is essential to help decision-makers understand how to make more efficient use of available resources, and is the primary focus of this paper. Wider issues regarding financing mental health care, such as tax-funded, universal health care provision, are complex, requiring strategies that involve trade-offs between affordability, targeting, access, equity and efficiency[4]. Again, therefore, there is a role for cost-effectiveness and associated evidence.

CURRENT ECONOMIC EVIDENCE AND KEY EVENTS IN MENTAL HEALTH CARE

Maternal mental health

Perinatal mental health is a good illustration of the potential "spillover" and "external" effects, and thus the wider economic impacts, of treatment and care in mental health. A recent review on cost-effectiveness of perinatal interventions for depression and/or anxiety looked at studies published between 2000 and 2017[17]. All eight studies reviewed targeted depression in postnatal mothers, while only one study included anxiety and fathers in the evaluation. Only four studies reported cost-utility findings to allow broader strategic comparison.

The authors concluded that screening-plus-treatment pro-

grammes are likely to be seen as cost-effective, with a cost per QALY ranging from £8,642[18] to £15,666[19]. These figures compare well with the cost-per-QALY threshold associated with NICE (£20,000), suggesting that the approach would be seen as representing value for money in the use of health care resources in England. Indeed, these findings probably underestimate the economic impacts of perinatal mental health care and treatment: the studies reviewed had a maximum time horizon of 2 years, and mostly only looked at health and social care costs rather than a wider societal perspective.

It is well known that perinatal depression can significantly affect child development up to 16 years of age[20]. These consequences are associated with substantial costs. An economic modelling study in the UK showed that 72% of the total costs of perinatal mental health problems is related to the child, and health and social care costs accounted only for £0.5 billion of a total annual cost of £8.1 billion[21]. Many of the costs are associated with productivity losses, education, criminal justice and quality of life deficits. Estimated total cost of one case of perinatal depression was the substantial sum of £73,822[21]. Economic evaluations that also consider the effects on the child would therefore provide further justification of treatment and care. These wider effects are, however, seldom included in current studies[4].

Economic evaluations of preventive strategies are emerging[22]. In a 2016 report on preventing postnatal depression[23], the authors concluded that midwifery-redesigned postnatal care may be cost-effective for universal prevention; and person-centred approach (PCA)-based and interpersonal psychotherapy (IPT)-based interventions for indicated prevention. More recently, health visitor training for women at risk of depression[19] has been evaluated for lower-risk women, with results suggesting high cost-effectiveness in preventing postnatal depressive symptoms[24]. Research into these promising areas is needed for more conclusive recommendations.

Other economic evidence gaps in this area include perinatal anxiety, antenatal depression, and interventions for fathers[17], as well as interventions in lower-resource settings. The latter is particularly needed, given that economic evidence generated in high-income areas is often not applicable. For example, although screening-plus-treatment programmes were shown to be cost-effective[17], this was based on evidence from high-income countries.

Routine screening in LMICs may overwhelm a weak health system and not represent the best use of resources[25]. Different service models, such as task-shifting, may also be needed. For example, psychosocial interventions delivered by non-specialists in antenatal health care facilities have demonstrated effectiveness in LMICs, although cost-effectiveness data are lacking[26].

Child and adolescent mental health

Mental health problems in childhood and adolescence are similarly associated with wide and enduring clinical and economic impacts. Progress in economic evidence development in this area remains slow. More evidence is available on psychosis early intervention[27], which often also covers an adult population and is reviewed later in this paper.

A 2014 review[28] noted a publication rate of all cost-related papers of approximately 10 per year between 2009 and 2014, with most studies coming from the US or UK. The author concluded that most questions concerning the economic implications of care and treatment for child and adolescent mental health (what, when, where, to whom, and how) remain unanswered, leaving stakeholders with insufficient information to support resource allocation decisions. The lack of cost-effective evidence is similarly noted in another recent review[29] and a report in 2016 on new economic evidence around the potential impact of youth mental health services[30].

Economic evidence is available for depression treatment in adolescents, although it remains inconclusive whether selective serotonin reuptake inhibitors (SSRIs) alone or SSRI plus cognitive behavioural therapy (CBT) is more cost-effective[28], with two earlier randomized controlled trials (RCTs) providing conflicting evidence[31,32]. In another review, the authors noted that, in children and adolescents, CBT is unlikely to be cost-effective compared with medication[33]. When CBT is used as second-line intervention for depressed young people declining antidepressants, a recent RCT has suggested dominance of CBT over treatment as usual by the end of 24 months, but not 12 months[34].

What can be noted from these studies is again the importance of time horizon, especially as economic evaluations embedded within RCTs usually have short follow-up periods. In one of these studies with follow-up at 12 and 36 weeks, the cost-effectiveness findings reversed between the two time-points: the shorter follow-up suggested SSRI treatment was more cost-effective, whereas the longer follow-up showed that SSRI plus CBT was more cost-effective[32,35]. An illustrative example of the enduring impact of childhood mental health problems is the long-term consequences of bullying that can be observed in adulthood, requiring long-term follow-up to understand the economic aspects of interventions on these consequences[36,37].

A recent literature review of economic evaluations published between 1997 and 2014 in the UK National Health Service (NHS) Economic Evaluations Database and other sources focused on attributes of care systems (i.e., excluding pharmacological or individual psychological therapies). Forty studies with both costs and outcomes of youth mental health care were identified[27]. These interventions targeted a wide range of mental health problems, including anxiety, depression, eating disorders, psychosis, substance use disorders, unspecified mental health problems, forensic mental health, and suicide and self-harm. Common attributes of interventions with favourable economic evidence were timely assessment strategies (including screening) and family-based interventions, although for the latter some variations existed as to whether there were other more cost-effective alternatives. Methodological problems in the literature were highlighted, including a narrow evaluation perspective, with none of the reviewed studies taking both a societal and a health care perspective[27].

A narrow health care perspective would miss a large part of the overall cost implications in addressing child and adolescent

mental health needs, which include impacts in the education and justice systems, and on families and employment[28]. For example, in a 2017 UK report that included 15 studies, the 3-year mental health-related costs in young people aged 12 to 15 years averaged £1,778 per individual per year; 90% of this cost fell to the education sector[30]. The spillover effects of child and adolescent mental health on carers and family, given the evolving dependency relationship between the child and family members, is also significant yet understudied[38].

Some recent developments can be noted to address the paucity of economic evidence in this area. In 2017, the Greenwich Expert Group proposed directions for future research focusing on LMICs, to make suggestions for "a cost-effective mental health care system that optimally improves the future outcomes of children and adolescents"[39].

Economic evaluation can now be seen as an integral component in major youth mental health initiatives, such as headspace (the National Youth Mental Health Foundation) in Australia[40]. Recognizing the cost implications of childhood mental health problems in adulthood, managed transition from child and adolescent to adult mental health service is being evaluated in the UK, with an embedded CUA as the primary economic analysis, in an ongoing nested cluster RCT[41].

Depression and other common mental disorders

As one of the most well-studied interventions for depression and anxiety, CBT has been frequently evaluated in economic analyses. In a systematic review of CUA from 22 studies published between 2004 and 2012 on CBT for major depressive disorder, the authors concluded that most studies showed "acceptable incremental cost-utility ratios"[33].

More specifically, the review suggested that individualized CBT is likely to be cost-effective both in combination with medication compared with medication alone and as standalone therapy compared with usual care, community referral, or bibliotherapy. Individualized CBT is also not inferior to medication (SSRIs and tricyclic antidepressants, TCAs), with interventions involving individualized CBT either being dominant or showing an ICER ranging from US$1,599 to US$46,206 per QALY.

For group CBT, similar results were suggested, with group CBT being cost-effective compared with SSRIs, TCAs, usual care, and bibliotherapy. Results for computerized CBT were more mixed. One of the limitations highlighted is the relatively short time horizon in the reviewed studies (average 19 months), bearing in mind that time to recovery in depression could be much longer[33].

More recently, research has suggested behavioural activation (BA) as a potential alternative to CBT that is less dependent on the skills of the therapist, which would be important for implementation in settings where mental health human resources are particularly scarce (e.g., many LMICs). In a recent trial comparing the cost and outcome of BA versus CBT, the authors found BA to be more cost-effective[42]. In their sensitivity analyses, with both wider societal perspectives (e.g., including productivity losses) and narrower perspectives (e.g., mental health service) considered, BA had a high probability of dominating and of being cost-effective at a willingness-to-pay threshold of £20,000-30,000 per QALY.

An issue related to better use of resources, especially highly skilled specialist human resources, is the cost-effectiveness of stepped care[43] or (stepped) collaborative care[44]. These have recently been reviewed, although evidence remains inconclusive, due partly to methodological issues (e.g., use of QALY as outcome measure, and a wide range of time horizons, from 6 to 24 months) and partly to the heterogeneity of these models.

In the review of studies on cost-effectiveness of stepped care for the prevention or treatment of depression and/or anxiety, four studies focused on treatment. The pooled analysis suggested cost-effectiveness of stepped care over care as usual in the treatment of anxiety but not depression[43]. In the review of 19 studies of (stepped) collaborative care for depressive disorders, cost-effectiveness ranged very widely: from dominance to an ICER of US$874,562 per QALY[44].

In 2016, Chisholm et al[45] published an ROI analysis on scaling up treatment for depression and anxiety in 36 countries between 2016 and 2030. The authors used projection modelling to investigate the treatment effects of depression and anxiety disorders, taking into consideration the economic outcomes of returning to work, absenteeism, and presenteeism rates, and suggested a benefit-to-cost ratio of 2.3-3.0 to 1, or 3.3-5.7 to 1 when the value of health returns (monetized healthy life years gained) was also considered. Not all benefits have been captured in this analysis, however, such as reduced welfare support, treatment and adherence for related physical health problems (e.g., coronary heart disease), and improved outcomes for family members and others who may be affected[45].

The monetary values attached to healthy life years might also generate some discussion. While savings in public finances from increased productivity and healthy life years when treating these common mental disorders may not be the primary concern of the mental health service sector that finances these treatments (i.e., silo mismatch, in which interventions may have impacts in multiple sectors, leading to a need to find cross-agency compensation arrangements – see below), there are probably large enough health care savings to cover the intervention costs.

Based on England's Improving Access to Psychological Therapies (IAPT) experience, which costs a one-off £650/person on average, Layard and Clark[46] argued that it "costs nothing" to the government. This argument was based on the consideration that 1% of the working age population is on disability benefits (and therefore paying reduced taxes) due to anxiety and depression, costing the government £650 per person-month, and, if they also require physical health care, the extra health care cost would be £750 per person-year for those not on IAPT. Scaled-up evidence-based psychological therapies would therefore, they argue, pay for themselves even if account was only taken of welfare benefits and health care costs[46].

Psychosis and other severe mental illnesses

Since deinstitutionalization in many countries dating back to the 1970s, to the introduction of early intervention services (EIP) around the 1990s, and the more recent recovery movement, severe mental illnesses (SMIs) have been at the forefront of major developments in mental health care and treatment, as well as a focus of economic evaluation. The complexity and chronicity of SMIs, however, pose challenges in both clinical and economic research, with large evidence gaps remaining with regard to the cost-effectiveness of these services.

Several meta-analyses have shown EIP to be effective in reducing costly outcomes such as hospitalization, bed-days and relapse rate, and in improving school or work involvement, as compared with treatment as usual[47-49]. A 2014 report published by Rethink Mental Illness[50] suggested that EIP and community-based interventions generate economic gains mainly by their effects on relapse, reduced need for expensive care, and wider recovery outcomes (e.g., employment, housing, and physical health).

Using analytical models to compare EIP with care as usual for people with first-episode psychosis[51], results showed that EIP could save around £2,000 per person over 3 years because of improved employment and education outcomes, and approximately £1,000 per person over 4 years because of reduced suicide rates. More recently, a systematic review of 16 studies found consistent evidence of cost-effectiveness of EIP in people with first-episode psychosis or clinical high risk for psychosis, compared with care as usual[52].

However, the authors cautioned that the evidence was of moderate methodological quality, with significant heterogeneity, and came mainly from high-income countries. In LMICs, for example, it remains unknown whether specialist EIP would be practicable and similarly cost-effective. There are also unanswered questions regarding service duration, delivery, and other parameters[53] of this complex intervention that could have clinical and cost implications.

Some economic evidence is available on interventions with more specific treatment targets, such as CBT for psychosis, medication adherence interventions, and supported employment. In a recent Health Technology Assessment report that included a systematic review on the cost-effectiveness of individual or group CBT for psychosis[54], six RCTs with economic evaluation were identified, which covered both people with first-episode psychosis and chronic or treatment-resistant psychosis.

Compared with treatment as usual (interventions that typically involve medication, counselling, community care, and case management), adding CBT for psychosis dominated for symptom or functional improvement. Two of the studies that included QALY as an outcome found an ICER ranging from £1,455 to £18,844 per QALY gained. However, the time horizons of these studies were short: between 9 and 18 months only. The authors of the report, therefore, conducted a microsimulation modelling study using a decision analytic model, with a time horizon of 5 years, concluding that adding CBT to usual treatment for people with psychosis again appeared to be a cost-effective option.

Among interventions that promote antipsychotic medication adherence, a strategy involving financial incentive has been evaluated favourably for cost-effectiveness. In a cluster RCT, people with schizophrenia, schizoaffective disorder or bipolar disorder were paid a modest financial incentive of £15 per depot injection. Results showed a cost of £982 to achieve a 20% increase in medication adherence and £2,950 for achieving "good" adherence, suggesting that this is likely to be seen as a cost-effective intervention[55].

For supported employment, the model with most economic evidence is Individual Placement and Support (IPS). In an RCT with CEA across six European countries, IPS led to better outcomes in terms of both days worked in competitive settings and percentage of people who worked at least 1 day, with results suggesting it to be almost certainly more cost-effective than standard vocational rehabilitation services[56].

In a review of 15 RCTs on the generalizability of IPS within and outside of the US[57], while noting a higher rate of competitive employment rate in the US than non-US studies (62% vs. 47%), the authors concluded that there are consistent positive outcomes that strongly favour IPS internationally. One of the economic considerations is the enormous costs associated with developing and maintaining non-competitive job programmes, which are usually borne by governments. Together with tax-exemption arrangements, these alternative supported employment programmes are often unsustainable economically.

Employment is an important target not only for the economy but also for a personal recovery goal or outcome. A recent paper on recovery and economics[58] reviewed the economic evidence for a range of recovery-focused approaches, including peer support, personal budgets, self-management, welfare and debt advice, joint crisis plans and advance directives, supported housing, and recovery colleges. Albeit patchy in terms of methodological robustness, available economic evidence does consistently support a recovery-focused approach.

This movement towards personal recovery poses questions about meaningful outcome measures, from clinical, economic and policy perspectives. In a systematic review of 59 studies on economic models and utility estimation methods in schizophrenia[59], the majority of models used QALYs or DALYs as value drivers, while others used Positive and Negative Syndrome Scale (PANSS) scores as the basis of utility estimations.

As noted in another systematic review on EIP, indicators that are more valued and relevant to people, health and care systems, and policy makers – such as social recovery, budget impact analyses, and equity measurements – are beginning to be included in the research agenda[52], although issues such as non-cashable savings and silo mismatches would be some of the foreseeable challenges with these outcome measures (see below).

Mental health in older persons: dementia and depression

Dementia care and intervention strategies are wide-ranging, including those targeting the person and/or the family or other

unpaid carers. Although cost-effectiveness studies were once considered "rare"[60], economic evidence is beginning to flourish. There is now good economic evidence concerning anti-dementia medications, antipsychotics and antidepressants. With cholinesterase inhibitors becoming available at generic price, more recent analyses show that they are more cost-effective as monotherapy than placebo ("best supportive care"), and probably also cost-saving for people with mild-to-moderate Alzheimer's disease (AD)[61].

For people with moderate-to-severe AD, a recently published trial offered new economic evidence. The cost-effectiveness of donepezil continuation compared to discontinuation was demonstrated when looking at each of a number of outcomes – cognition, functioning (activities of daily living), and QALYs – and whether costs measured only health and social care service use or additionally unpaid care[62]. It also reduced the risk of nursing home placement after 1 year (but not 4 years)[63].

There is very little other economic evidence on the cost-effectiveness of combinations of medications for treating AD. There is no economic case for using antidepressant medication to treat people with AD who have comorbid depression. The most thorough study of antidepressant medication for people with probable or possible AD and comorbid depression was the Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial[64]. The economic evaluation embedded within the trial found no significant differences in costs for any hospital-based or community health or social care services between the groups over 39 weeks[65]. There were also no differences in QALYs over this period.

Similarly, there is no economic case for using antipsychotic medications to treat the psychological and behavioural symptoms of dementia. The strongest evidence comes from the Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study, conducted across 42 US sites. This trial looked at the clinical and economic case for three widely used antipsychotics (olanzapine, quetiapine and risperidone) compared to placebo using a double-blind RCT design that included people with AD who experienced hallucinations, delusions or agitation. Costs over a 9-month period were lower for the placebo group than for any of the groups treated with antipsychotics[66]. The only outcome difference found in the trial was that placebo was better than olanzapine in relation to activities of daily living. In other words, antipsychotic treatment was not cost-effective.

The 2018 NICE guidelines[67] on interventions to promote cognition, independence and well-being recommended offering "a range of activities to promote well-being that are tailored to the person's preferences" and "group cognitive stimulation therapy to people living with mild to moderate dementia". Relevant economic evidence for these two recommendations is available from studies on cognitive stimulation therapy (CST) and tailored activity program (TAP).

Economic evaluations of group CST[68] and maintenance CST[69] found that the intervention is good value for money, as the improvements in cognition and quality of life were large enough, while the additional cost for providing CST is relatively modest. The latter appears to be most cost-effective in those living alone and/or having better cognition[70]. Cholinesterase inhibitors enhance the effects of maintenance CST and improve its cost-effectiveness[69].

Using simulation modelling, NICE conducted an economic analysis of CST, with results showing an ICER under £20,000 per QALY[71]. For TAP, an earlier cost-effectiveness analysis suggested an ICER of US$2.37 per day for the carer to save one hour in doing things for the person with dementia, and US$1.10 per day to save one hour in being "on duty".

Good evidence is also available for multicomponent carer support programmes, such as the STrAtegies for RelaTives (START) in the UK and the Resources for Enhancing Alzheimer's Caregiver Health (REACH, and the newer REACH II) in the US.

Carers in the START programme used fewer services in the first 8 months, which offset the cost of the programme. When considered together with other positive outcomes, START is cost-effective in the short term[72]. The long-term follow-up results have just become available. At 6-year follow-up, carer mental health outcomes were better in the intervention group, but neither patient-related nor carer-related costs were different between groups[73]. START is therefore clinically effective for at least 6 years without increasing costs.

Findings from the REACH II programme have similarly suggested effectiveness and cost-effectiveness, with ICER analysis showing a US$5 per day for one hour saved from caregiving[74]. Despite these cost-effectiveness findings, some authors have raised concerns about the lack of funding to support wider implementation[75].

The (cost-)effectiveness of dementia care management (DCM) remains inconclusive, due to protocol and research methodological differences (e.g., short observation period, different definition of DCM). In a recent RCT investigating a DCM model involving primary care physicians (Dementia: Life- and Person-Centered Help, DelpHi)[76], results suggested that DCM is cost-effective (dominant) compared with usual care, especially among people with dementia living alone. Reduced hospitalization and delayed institutionalization are likely contributors to this cost-effectiveness finding. The authors, however, noted that their positive findings differed from some previous trials, which could be attributable to the milder cognitive impairment in their sample[76], suggestive of better cost-effectiveness with earlier intervention.

Several studies provide evidence on the cost-effectiveness of care home intervention programmes, including two major trials from the UK: the Managing Agitation and Raising Quality of Life (MARQUE)[77] and the Well-being and Health for people with Dementia (WHELD)[78]. The MARQUE study demonstrated cost-effectiveness in terms of QALY gained, but it was not efficacious in managing agitation[77]. The WHELD intervention, person-centred care that incorporated antipsychotic review, showed benefits in both agitation and quality of life, suggestive of a cost-saving

model even with a relatively small effect size[79]; with the additional cost of the programme offset by the higher health and social care costs in the treatment as usual group[78].

Very few studies have looked at cost-effectiveness of interventions targeting later-life depression. A recent review noted that cost-effectiveness data were available from two stepped care prevention studies, with one study suggesting that stepped care prevention is not cost-effective compared with care as usual, whereas the other showed that the incidence rate of depression and anxiety in older persons was cut by half with the prevention programme, increasing depression/anxiety-free life years at an affordable cost.

The authors noted that, in older populations, economic evaluations would disregard productivity loss, with the assumption that it is irrelevant[43]. With population ageing and the associated increase in prevalence of mental health problems in old age, this raises the question of affordability – even when interventions are cost-effective and potentially worth investing – and more value-laden issues such as inequalities and parity between mental health and physical health[80].

CHALLENGES AND RESPONSES

Challenges

Economic evidence cannot make decisions, but it can make decisions better informed. However, challenges emerge when attempting to move from evidence to recommendations to action to impact (see Figure 1).

The first of these is simply gaps in the evidence base. Despite rapid growth in cost-effectiveness and related studies in recent years, some areas remain unexplored. For example, we have limited understanding beyond the short term of the economic consequences of mental illness or of treatments for it. There are few economic evaluations of ways to protect individual rights or support recovery. Prevention and early intervention also remain relatively neglected[81].

Economics research on families is rare, despite the parts they play in aetiology, support and recovery. There is also little on efforts to address wider societal aspects of mental illness, such as poor awareness, discrimination and stigma[82]. Most glaring of all, of course, is the scarcity of economic evidence in LMICs, as we pointed out in many of the condition-specific sections above.

Even when evidence exists, it may not be robust enough to build reliable policy or practice recommendations. Relatedly, the available evidence may not be transferable from the context in which it was gathered to other contexts (especially to other countries): cost-effectiveness evidence "travels less well" than most clinical evidence.

A second challenge is where an intervention is cost-effective (i.e., generating outcomes considered sufficient to justify the higher costs of achieving them) but is unaffordable because there is no money left in the budget or no suitably skilled staff available to deliver it. This is why strategic decision-makers are always keen to hear about new interventions that achieve equiv-

Figure 1 Challenges and responses in mental health economics. LMICs – low- and middle-income countries

alent or better outcomes compared to standard care but at lower cost: hence, for example, interest in BA rather than CBT for depression[42], and the recent finding of cost-savings with DCM, especially among people with dementia living alone[76]. Therapeutic breakthroughs (e.g., medications with new modes of action) may promise disease modification, fewer symptoms or better quality of life, but if they are not simultaneously cost-reducing they put added pressure on already over-stretched health care budgets.

A related challenge is that apparent savings found in a research study might not prove "cashable" in the real world. Early intervention psychosis teams might shorten inpatient stays[47], but will not generate actual savings unless inpatient beds close or staff are shed. Effective support for carers might reduce their time inputs (to which an evaluation might attach costs) or stress levels[73], but might not release resources transferable to other uses.

Effective treatments for mental illness might have substantial consequences outside the immediate treatment setting. There might be cost reductions in other clinical areas if treatment of a mental illness helps patients manage their comorbid conditions better, for example[83]. If different specialties then have separate budgets, it might be hard to align costs and benefits so as to make the treatment appear economically attractive.

More complicated still is when good mental health treatment has its greatest impacts (economic or other) outside the health sector. The highest public sector costs of childhood mental illness are in schools[84], yet treatment is mostly a health care sector responsibility. The biggest cost consequences of perinatal maternal mental illness stem from the risks of long-term emotional, behavioural and cognitive damage to the child[20]. Effective depression treatment has bigger effects on employment-related costs than health care costs[85]. By far the largest long-term cost consequences of childhood conduct disorder are linked to criminality[86]. None of these is surprising, but each generates the potential "silo budgeting" disincentive to choose the most efficient overall course of action.

Some economic effects of mental illness and treatment may be missed. Mental illness may interfere with an individual's ability to complete his/her education, participate in family life, or be fully productive in the workplace. It may impact, as just noted, on the health and wealth of family members and unpaid carers. Although less "visible" in some sense, these effects may nevertheless be pivotal in shaping lives and generating well-being. The challenge is to ensure that economic evaluations measure these wider impacts (i.e., take a societal perspective), and (especially) that users of evaluation findings take these impacts into account in decision-making. For example, ignoring the often considerable economic and other burdens faced by carers could undermine community models of care, whilst ignoring productivity losses in research and policy could harden employer attitudes to mental illness.

The chronicity of many mental illnesses means that their economic consequences could be long-term, and equivalently the full pay-offs from better treatment might not be seen for some years. This makes it harder not only to demonstrate the economic case for prevention, but also to persuade decision-makers working to shorter time-scales (linked, perhaps, to election cycles) to invest now even though the gains eventually could be substantial[87,88]. Together, the challenges of this timing and "silo budgeting" create the pernicious complication of "diagonal accounting": the double disincentive that spending on an intervention by one sector now generates savings (or other benefits) mainly in other sectors and mainly in future years.

The final set of challenges emerging from the growing body of economic evidence relates to the interconnected issues of diversity, disadvantage and discrimination. Published results from research are dominated by what happens on average: mean improvement in the primary outcome, mean cost difference, overall cost-effectiveness ratio, for instance. Those published studies will, of course, also report variations around those averages, yet rarely will there be much discussion of what happens on the margins of the study sample, and even more rarely will there be replicated or reported analyses for subpopulations.

What might be effective or cost-effective on average might be ineffective (perhaps even damaging) or inaccessible for certain cultural or social groups. Economically disadvantaged individuals generally do not have the same access to services as wealthier individuals, especially if payment is required. This is particularly important given that mental illness is strongly linked to social and economic marginalization[89,90]. Yet inequalities – between socioeconomic, religious, cultural, ethnic and other groups, between genders and linked to age – simply do not get the attention they deserve in the economics literature, just as they tend to be ignored in large swathes of the clinical literature.

Responses

What, then, should be the responses? One obvious recommendation to the research community is to build up the evidence base. Indeed, it is pertinent to ask: in what circumstances would it make sense to conduct a clinical trial or other treatment effectiveness study and to *exclude* an economic evaluation component? Somewhere down the track a decision-maker is surely going to want reassurance that an effective intervention is affordable and makes good use of available resources. Given the tiny cost of adding an economics element into (say) a clinical trial, it should be the default option to include a cost-effectiveness or similar analysis, and not the exception.

Mental illness is very much an individual experience and certainly a health sector responsibility, yet it needs society-wide attention and cross-government action. The multiple impacts of mental illness – which could be felt across many aspects of an individual's life – lead to numerous challenges. Different medical specialties need to be better at coordinating their treatments, given that many mentally ill people have other long-term conditions[91]. Different parts of government should not merely be aware of mental illness, but active in its prevention and appropriately responsive when it emerges. This applies to policy in the fields of education, employment, social care, housing, criminal justice, poverty alleviation, social security (welfare) benefits,

community development, immigration and beyond.

Moreover, across different policy domains, efforts need to be made to ensure that individuals do not "fall between the cracks"[92]. This is especially germane with respect to population groups that are already socially or economically marginalized. Mental health policy must include strategies for tackling unacceptable inequalities in ill-health, education and employment-related opportunities, access to treatment and quality of life[89]. In the wider context, this surely argues for universal health coverage and (within it) parity between physical and mental health. Moreover, the heterogeneity of circumstances, experience, outcomes and costs argues for policy frameworks and treatment programmes that recognize and respond appropriately to individual strengths, needs and aspirations[93]. Inter alia, this lends support to recovery-oriented approaches, particularly given the economic evidence in support of them[50], and other modes of devolved decision-making such as personal budgets[94].

Coordination of action across different entities (individuals, families, communities and organizations) as well as across sectors (both public and private) is never easy and may require some form of cross-agency compensation: the "gainers" (those who enjoy short- or long-term savings or other benefits) compensating the "losers" (those whose budgets are used to pay for effective treatment or care). More challengingly, the "gainers" and "losers" need to find ways to overcome the "diagonal accounting" challenge: encouraging investment not only across budgets but for the long term. This is exactly the kind of situation where government needs to step in, playing a strong leadership role in bringing different areas of public policy together and emphasizing (indeed, possibly financing) those investments whose pay-offs are mainly some way into the future.

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Dopamine and glutamate in schizophrenia: biology, symptoms and treatment

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Glutamate and dopamine systems play distinct roles in terms of neuronal signalling, yet both have been proposed to contribute significantly to the pathophysiology of schizophrenia. In this paper we assess research that has implicated both systems in the aetiology of this disorder. We examine evidence from post-mortem, preclinical, pharmacological and in vivo neuroimaging studies. Pharmacological and preclinical studies implicate both systems, and in vivo imaging of the dopamine system has consistently identified elevated striatal dopamine synthesis and release capacity in schizophrenia. Imaging of the glutamate system and other aspects of research on the dopamine system have produced less consistent findings, potentially due to methodological limitations and the heterogeneity of the disorder. Converging evidence indicates that genetic and environmental risk factors for schizophrenia underlie disruption of glutamatergic and dopaminergic function. However, while genetic influences may directly underlie glutamatergic dysfunction, few genetic risk variants directly implicate the dopamine system, indicating that aberrant dopamine signalling is likely to be predominantly due to other factors. We discuss the neural circuits through which the two systems interact, and how their disruption may cause psychotic symptoms. We also discuss mechanisms through which existing treatments operate, and how recent research has highlighted opportunities for the development of novel pharmacological therapies. Finally, we consider outstanding questions for the field, including what remains unknown regarding the nature of glutamate and dopamine function in schizophrenia, and what needs to be achieved to make progress in developing new treatments.

Key words: Psychosis, schizophrenia, dopamine, glutamate, antipsychotics, striatum, NMDA receptors, D2 receptors, D1 receptors, dorsolateral prefrontal cortex, GABA interneurons, amphetamine, ketamine, cognitive symptoms

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Schizophrenia is a severe mental disorder characterized by positive symptoms such as delusions and hallucinations, negative symptoms including amotivation and social withdrawal, and cognitive symptoms such as deficits in working memory and cognitive flexibility[1]. The disorder accounts for significant health care costs, and is associated with a reduced life expectancy of about 15 years on average[2].

Antipsychotics were serendipitously discovered over fifty years ago, but it took another decade or so until dopamine antagonism was demonstrated as central to their clinical effectiveness[3]. Further evidence implicating the dopamine system in the pathophysiology of schizophrenia has subsequently accumulated, and it remains the case that all licensed first-line treatments for schizophrenia operate primarily via antagonism of the dopamine D2 receptor[4].

However, despite the central role that dopamine plays in our understanding of schizophrenia, it has also become increasingly clear that dysfunction of this system may not be sufficient to explain several phenomena. In particular, dopamine blockade is not an effective treatment for negative and cognitive symptoms and, in a significant proportion of patients, it does not improve positive symptoms either. As a result, attention has turned to additional neurochemical targets. Glutamate is the major excitatory neurotransmitter of the central nervous system. The finding that antagonists of a specific glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor, induce psychotic symptoms has led to a wealth of research implicating the glutamate system in the pathophysiology of schizophrenia.

In this paper we review the evidence regarding dopaminergic and glutamatergic functioning in schizophrenia. We survey indirect findings from preclinical, genetic and pharmacological studies, evidence from post-mortem research, and results of neuroimaging studies that characterize functioning in living patients. We discuss how dysregulation of these systems may lead to the symptoms of the disorder, and the therapeutic possibilities associated with their pharmacological modulation. We then explore what may underlie this dysregulation, and the interaction between the two systems, before concluding by considering outstanding questions for the field.

DOPAMINE

Dopamine was initially thought to be a biologically inactive intermediary compound on the synthetic pathway between tyrosine and noradrenaline. Work by A. Carlsson and others, however, demonstrated that dopamine depletion inhibited movement, and that this effect could be reversed following the administration of the dopamine precursor L-DOPA. This established that the molecule was of major biological importance in its own right[5], and discrete dopaminergic projections were subsequently identified.

That dopaminergic dysfunction might play a role in the development of psychotic symptoms is one of the longest standing hypotheses regarding the pathophysiology of schizophrenia. Below, we discuss the evidence for dopamine dysfunction in

schizophrenia, before considering how this may lead to psychotic symptoms, and the mechanisms through which dopamine modulating treatments exert their effects.

Indirect evidence for dopamine dysfunction in schizophrenia

Animal models

Rodent models of schizophrenia are useful for investigating molecular mechanisms that may be of pathophysiological relevance, and for testing novel therapeutic interventions.

One well characterized model of dopaminergic hyperactivity involves administering repeated doses of amphetamine. This has been shown to induce events that are also observed in individuals with schizophrenia, such as reduced prepulse inhibition, stereotyped behaviours, and impaired cognitive flexibility and attention[6]. Given that amphetamine results in dopamine release, and that the above effects can be ameliorated with the administration of dopamine antagonists, this provides indirect evidence for a role of dopamine in behaviour thought to be a proxy for psychotic symptoms.

Another example is that of mice genetically modified to overexpress dopamine D2 receptors in the striatum, which also display a wide range of schizophrenia-like behaviours[7]. Similarly, transgenic insertion of tyrosine hydroxylase and guanosine triphosphate (GTP) cyclohydrase 1 into the substantia nigra in early adolescence increases dopamine synthesis capacity, and has been associated with a schizophrenia-like behavioural phenotype[8].

Other examples do not target the dopamine system directly, but are still associated with dopaminergic abnormalities. The methylazoxymethanol acetate (MAM) model involves inducing neurodevelopmental disruption of the hippocampus via the administration of MAM to pregnant rats, and is accompanied by increased firing rates of mesostriatal dopamine neurons[9]. A model of environmental risk factors in which rats were socially isolated post weaning has also been associated with increased striatal presynaptic dopamine function[10].

In summary, multiple methods have been used to induce increased striatal dopamine signalling in animal models, and these consistently produce behaviours analogous to those observed in individuals with schizophrenia.

Cerebrospinal fluid and post-mortem studies

Studies examining levels of dopamine and its metabolites – 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) – in schizophrenia, both peripherally and in cerebrospinal fluid (CSF), have given inconsistent results[11-13]. This may be due to the fact that these levels are a state dependent marker, and to the effects of antipsychotic treatment. Studies have found that levels of dopamine, HVA and DOPAC in CSF are only increased in those receiving antipsychotic treatment[13,14], and that reductions occur following the withdrawal of antipsychotics[15,16].

Some[17-19], but not all[20], studies of HVA have found higher levels in both CSF and plasma of acutely relapsed patients compared to stable patients. There have also been suggestions that baseline plasma HVA levels may predict subsequent response to antipsychotics, which shows some parallels with imaging findings considered below[21].

This approach to studying the dopamine system, however, has declined in popularity over recent years. A major weakness is that the measurement occurs distal from the dopamine neurons of interest. Since both hypo- and hyperdopaminergic function may exist within an individual simultaneously, a technique that allows for anatomical specificity is required to understand the nature and localization of changes.

Early post-mortem investigations suggested that striatal D2 receptor levels might be raised in individuals with psychosis[22], and a meta-analysis of seven post-mortem studies suggested that receptor levels were increased with a large effect size[23]. However, no studies of antipsychotic naïve individuals exist, and the majority are of individuals chronically treated with antipsychotic medications, which have been found to lead to D2 receptor upregulation[24,25].

Post-mortem studies have also examined the substantia nigra. In these studies evidence regarding dopamine function is inconsistent, with some studies suggesting an increase in tyrosine hydroxylase levels in patients[26], but others finding no difference[27,28]. Other studies have found abnormal nuclear morphology of substantia nigra neurons[29], reduced dopamine transporter (DAT) and vesicular monoamine transporter (VMAT) gene expression, and increased monoamine oxidase A expression[28].

Recent collaborative efforts in amassing significantly larger post-mortem sample sizes, and applying more sophisticated methods of analysis, may improve our understanding in the near future[30]. However, even with these developments, the drawbacks of post-mortem studies include heterogenous tissue quality, the fact that the majority of samples are from older patients with a long history of antipsychotic use, limited information regarding clinical phenotype, and that death itself leads to a wide range of neurobiological changes that may obscure important differences.

Studies in living participants have greater potential to include younger individuals, drug-free subjects, and also the ability to look at within-individual changes in symptoms and how these relate to pharmacological manipulation.

Psychopharmacology of dopaminergic agonists and antagonists

The discovery that chlorpromazine and reserpine were effective in the treatment of schizophrenia occurred prior to the identification of dopamine as a neurotransmitter. It was not until the 1970s that the clinical potency of antipsychotics was incon-

trovertibly linked to blockade of the dopamine D2 receptor[31,32]. In addition, selective D2 antagonists show equivalent efficacy to drugs with a broad spectrum of activity[33], indicating that D2 antagonism is sufficient for antipsychotic efficacy.

It was also noted that drugs such as amphetamine that increase dopaminergic neurotransmission could induce psychotic symptoms in healthy individuals, and exacerbate psychotic symptoms in individuals with schizophrenia[34,35]. Similarly, L-DOPA treatment in Parkinson's disease has been found to induce psychotic symptoms in some individuals[36]. However, while amphetamine-induced psychosis is marked by hallucinations, delusions, paranoia, and conceptual disorganization, it is not typically associated with negative and cognitive symptoms of the same form as those observed in schizophrenia[37]. This relative specificity to positive psychotic symptoms contrasts with glutamatergic models of schizophrenia (see later).

Summary of indirect findings

The findings discussed above provide evidence that aberrant function of the dopamine system contributes to psychotic symptoms (see Table 1). However, these methods are unable to identify where within the brain this dysfunction is localized to and, for the most part, cannot provide a direct link to symptoms. We next discuss methods for in vivo imaging of the dopamine system, which has the potential to overcome these obstacles.

Imaging dopamine in vivo

Both magnetic resonance imaging (MRI) and positron emission tomography (PET) have been used to characterize the dopamine system in vivo (Table 2). PET provides molecular specificity to the dopamine system, but this comes at the cost of lower temporal and spatial resolution compared to MRI.

MRI

Although MRI lacks the ability to directly image the dopamine system, recent work imaging neuromelanin has shown some promise in quantifying the dopamine system in vivo. Neuromelanin is synthesized via iron dependent oxidation of cytosolic dopamine, and accumulates in dopamine neurons of the substantia nigra. It has been demonstrated that the neuromelanin MRI signal is associated with integrity of dopamine neurons, with dopamine release capacity in the striatum, and with the severity of psychosis in schizophrenia[49].

Functional MRI (fMRI) has also been used in attempts to infer functioning of the dopamine system. Task-based fMRI has been adopted to quantify the striatal response to reward, and this has been linked to dopamine function, although the precise relationship is complex[50]. There is consistent evidence of reduced ventral striatal activation to reward in schizophrenia[51]. We consider how this is consistent with the hypothesis of an overactive dopamine system in the section discussing psychotic symptoms below.

PET: dopamine receptors

Dopamine receptors have been studied using a wide range of radioligands. The majority of studies have used ligands specific for D2-type (i.e., D2, D3 and D4) dopamine receptors, although several studies have also examined D1-type (i.e., D1 and D5) receptors.

Table 1 Summary of indirect evidence for dysfunction of dopamine and glutamate systems in schizophrenia

	Dopamine	Glutamate
Animal models	Amphetamine administration, striatal D2 overexpression, and transgenically increased dopamine synthesis capacity are associated with schizophrenia-like behaviours. Models of neurodevelopmental and social risk factors are associated with increased striatal dopamine function.	Administration of NMDA antagonists induces a wide variety of schizophrenia-like behaviours. Genetic models that disrupt NMDA signalling (by reducing levels of D-serine, inactivating D-amino oxidase or decreasing dysbindin) show behavioural and neurobiological changes similar to those observed in schizophrenia.
Cerebrospinal fluid (CSF)	Studies of DOPAC and HVA both peripherally and in CSF have been inconsistent.	Studies of glutamate levels are inconsistent, but kynurenic acid (an NMDA antagonist) levels appear consistently raised.
Post-mortem studies	Increased D2 receptor densities have been observed, but may result from medication use.	Glutamate neurons show reduced dendrite arborization, spine density and synaptophysin expression. Glutamate transporter EAAT2 protein and mRNA levels appear reduced in frontal and temporal areas. There is some evidence that glutaminase expression is increased in patients, and also that GRIN1 abnormalities exist.
Pharmacological studies	Clinical potency of antipsychotics is strongly linked to their affinity for the D2 receptor. Amphetamines can induce positive psychotic symptoms in healthy controls and worsen symptoms in patients.	NMDA antagonists induce positive, negative and cognitive psychotic symptoms in healthy controls. Chronic ketamine users show subthreshold psychotic symptoms.

NMDA – N-methyl-D-aspartate, DOPAC – 3,4-dihydroxyphenylacetic acid, HVA – homovanillic acid, EAAT – excitatory amino acid transporter

Table 2 Summary of imaging studies of the dopamine and glutamate systems in schizophrenia

			Striatal	Extra-striatal
DOPAMINE	Dopamine receptors	D1	Few studies, and no differences consistently noted.	Studies using [^{3}H]SCH 23390 have reported decreased binding in patients; those using [^{11}C] NNC 112 reported an increase in patients.
		D2	No patient/control differences in unmedicated cohorts. Variability increased in patients.	Generally poor signal-to-noise ratio. No consistent patient/control differences.
	Presynaptic dopamine function		Consistently increased in both previously medicated and antipsychotic naïve patients (g=0.7). Patient-control differences appear greatest in the dorsal striatum.	Two studies have found increased synthesis capacity in the substantia nigra (although not observed in another). One amphetamine challenge study found reduced release in patients in prefrontal cortex. Psychological challenges have produced less clear results. Findings of challenge studies in the substantia nigra are inconsistent.
	Dopamine transport	DAT	No patient-control differences in mean binding, but variability increased in patients.	Fewer studies. Some suggestion that thalamic levels may be raised in patients.
		VMAT		Two studies have found increased levels in the ventral brainstem of patients.
GLUTAMATE	Basal ganglia		Glx (g=0.4) and glutamate (g=0.6) levels raised in patients.	
	Thalamus		Glutamine levels raised in patients (g=0.6).	
	Medial temporal lobe		Glx levels raised in patients (g=0.3).	

DAT – dopamine transporter, VMAT – vesicular monoamine transporter, Glx – glutamate + glutamine

Striatum

It has been proposed that excessive dopaminergic neurotransmission in schizophrenia results from upregulation of striatal postsynaptic D2-type receptors. However, meta-analyses of studies using PET show only a small increase in receptor density at most in schizophrenia, and there is no significant difference between patients and controls in analyses restricted to medication naïve patients[52]. When combined with evidence that antipsychotic treatment appears to lead to D2 receptor upregulation[24,25], it appears possible that any patient-control differences may be secondary to confounding by treatment.

There are caveats, however, to the above inference. First, the majority of studies are unable to measure the absolute density of receptors, because a proportion of receptors will be occupied by endogenous dopamine. If schizophrenia is associated with increased synaptic dopamine levels, this could mask a concurrent increase in receptor densities. Indeed, one study where dopamine depletion was undertaken prior to PET scanning showed significantly increased dopamine receptor availability in patients, although this increase was not significant in another study using this approach[53,54].

Second, the majority of ligands are selective for D2 over D3 and D4 receptors. The studies that have employed butyrophenone tracers (that have an affinity for D4 receptors in addition to D2 and D3 receptors) have tended to show raised receptor densities compared to those studies employing ligands that do not have D4 affinity[52]. In addition to potential differences in D2/3/4 subtype proportions, D2 receptors exist in both high and low affinity states, and some evidence suggests that schizophrenia may be associated with an increased proportion of receptors in the high affinity state[55-58].

Furthermore, following receptor internalization, some tracers remain bound, while others dissociate. So, if receptor internalization is increased in one group, this would register as reduced ligand binding if using a tracer that dissociates on internalization, but not if using a tracer that remains bound[59,60].

Finally, it has recently been shown that the *variability* of striatal D2 receptor levels is greater in patients than controls[61], suggesting that differences in D2 receptor density may exist, but only within a subgroup of patients, although whether this reflects a primary pathology or an effect of prior antipsychotic treatment in some patients remains unclear.

D1-type receptors have not been studied frequently in the striatum, and the studies that have been undertaken do not show any clear patient-control differences[52,62].

Extra-striatal regions

The measurement of dopamine receptors in extra-striatal regions is complicated by the lower receptor densities, which means

that the signal-to-noise ratio is much lower than in the striatum. Studies of thalamic, temporal cortex and substantia nigra D2/3 receptor availability have not consistently shown patient-control differences[63]. Other cortical regions have rarely been studied, and have not shown consistent changes[63].

D1 receptors have been more thoroughly examined in cortical regions than in the striatum. Two studies using [^{11}C]NNC 112 reported an increase in patients[64,65], while one reported a decrease[66]. Four studies using [^{3}H]SCH 23390 have reported a decrease[62,66-68], while two found no significant differences[69,70]. The interpretation of these findings is complicated by the fact that dopamine depletion paradoxically decreases the binding of [^{3}H]SCH 23390, while it has no effect upon [^{11}C]NNC 112 binding. Furthermore, antipsychotic exposure decreases D1 receptor expression, and both the above ligands also show affinity for the 5-HT$_{2A}$ receptor[71-73].

PET: dopamine transport mechanisms

DAT is involved in reuptake of dopamine from the synaptic cleft, and is often interpreted in PET studies as a measure of the density of dopamine neurons. Studies examining DAT density in the striatum have found no consistent differences between patients and controls[52], although, as with D2 receptors, variability is increased in schizophrenia, suggesting that differences may exist within a subgroup[61]. A more recent study did find significantly raised striatal DAT levels in patients, but this was observed in those with a chronic illness with long-term antipsychotic exposure[74].

There have been fewer studies examining extra-striatal regions, although the ones that have been undertaken do suggest that thalamic DAT levels may be raised in patients[74,75].

VMAT2 transports intracellular monoamines into synaptic vesicles. Two PET studies have found that its levels were increased in the ventral brainstem of individuals with schizophrenia, but found no differences compared to controls in the striatum or thalamus[76,77]. This is in contrast to the post-mortem studies discussed above[28], but in keeping with a study showing increased VMAT2 density within platelets from individuals with schizophrenia[78].

PET: presynaptic dopamine function

Multiple methods exist for quantifying aspects of presynaptic dopamine function.

Several studies have investigated dopamine release capacity by studying the reaction of the dopamine system to an acute challenge, be that pharmacological such as amphetamine, or psychological such as a reward or stress task[79]. Animal studies have shown that comparing ligand binding during the challenge to binding at baseline allows one to infer the amount of dopamine release induced by the task[80].

Alternatively, one can obtain a measure of baseline synaptic dopamine levels by comparing a baseline scan with a scan obtained following the administration of a dopamine depleting agent such as alpha-methylparatyrosine.

Finally, radiolabelled L-DOPA can be used to quantify dopamine synthesis capacity. Radiolabeled L-DOPA is taken up by dopamine neurons, where it is converted by aromatic L-amino acid decarboxylase to dopamine, which is then sequestered in vesicles within nerve terminals[81]. The rate of uptake provides an index of dopamine synthesis capacity.

Striatum

Studies have consistently demonstrated raised presynaptic dopamine function in schizophrenia, with Hedges' g=0.7 (Hedges' g is a measure of effect size, and values of 0.2 are typically considered small, those of 0.5 medium, and those of 0.8 large[82]). The studies using a challenge paradigm show larger effect sizes (g=1.0) compared to those quantifying dopamine synthesis capacity (g=0.5)[83]. The hyperdopaminergic state associated with schizophrenia appears greatest within the dorsal striatum[83].

Further evidence for pathophysiological relevance comes from studies showing a direct association between synthesis capacity and the severity of positive psychotic symptoms[84-86]. The relationship with other symptom domains is less clear: an inverse relationship with depressive symptoms[87] and a lower synthesis capacity associated with worse cognitive performance[88] have been reported.

Extra-striatal regions

Outside of the striatum, dopamine synthesis capacity can only be reliably measured in a limited number of brain regions, such as the substantia nigra and the amygdala, using current techniques[89]. Two studies have found increased dopamine synthesis capacity in the substantia nigra[90,91], although this was not observed in another[92]. One study also found raised dopamine turnover in the amygdala[91].

Although cortical dopamine receptors are predominantly D1-type, D1 receptor ligands are not reliably displaceable, and therefore not suitable for challenge or displacement studies. Cortical D2 receptors do exist, but studies are complicated by their sparsity[93]. Furthermore, although challenge paradigms have demonstrated validity in the striatum, the results of cortical studies are harder to interpret, with displacement not always observed[94].

One study using amphetamine challenge in combination with the high-affinity ligand FLB-457 found reduced dopamine release in the prefrontal cortex in individuals with schizophrenia[95]. Two other recent FLB-457 studies adopted psychological challenges. One of these used a psychological stressor, which did not induce cortical tracer displacement in either patients or controls[96]. The other used a cognitive test of executive function, which did show lower tracer displacement in patients, but interpretation was complicated by the fact that, again, the task did not consistently induce dopamine release[97]. A study using ^{18}F-fallypride found no differences between patients and controls in terms of stress-induced cortical dopamine release[98].

Two studies have examined dopamine release in the substantia nigra. One used a stress challenge and found an increased release in patients[99]; the other adopted an amphetamine challenge and found a non-significant reduction[95].

PET: dopamine across the psychosis spectrum

Several studies have investigated dopamine function in subjects at clinical high risk for psychosis. Initial studies showed evidence of raised presynaptic dopamine function in these individuals[100-102]. However, this was not seen in the largest study to date[103]. This may potentially result from the fact that raised presynaptic striatal dopamine function appears to be limited to those subjects who subsequently develop psychosis[104], and transition rates have declined in recent years.

A study of healthy individuals that experience auditory hallucinations also found no difference in striatal dopamine synthesis capacity compared to healthy controls without hallucinations[105]. Studies in individuals at increased genetic risk for schizophrenia, such as patients' relatives and individuals with 22q11.2 deletion syndrome, have also not shown consistent differences from controls in terms of presynaptic dopamine function[106-108].

Studies in psychotic individuals with diagnoses other than schizophrenia, such as bipolar disorder and temporal lobe epilepsy[86,109], have found raised striatal dopamine synthesis capacity. This finding, along with the inconsistent evidence in people at increased clinical or genetic risk, may suggest that increased striatal dopamine synthesis capacity is associated with psychosis across psychiatric diagnoses, rather than being an underlying risk factor for schizophrenia.

Studies of dopamine receptor densities in individuals at both clinical[99,100,110] and genetic[107,110-113] high risk are similar to those in individuals with schizophrenia, in that they have shown no clear differences from controls.

Summary of PET findings

The studies reviewed above provide consistent evidence of a striatal presynaptic hyperdopaminergic state in schizophrenia (see Table 2), and little consistent evidence of altered D2/3 receptor levels. It remains uncertain as to whether abnormalities exist with regard to other dopamine receptors, or with cortical dopamine function.

Consequences of dopaminergic dysfunction

Prediction errors, salience and positive symptoms

After its role in movement was established, preclinical findings suggested that dopamine also played a role in signalling reward[114]. Later work demonstrated that signalling more specifically related to the discrepancy between expected and received reward – a reward prediction error[115]. More recently, it has been demonstrated that firing is not exclusively tied to reward prediction, but rather can occur in response to a wide range of salient stimuli[116-120], and that in more dorsal regions of the striatum dopamine signalling is particularly associated with threat-related stimuli[118,119].

Several related theories have proposed how disruption to normal dopamine function could underlie positive psychotic symptoms such as delusions and hallucinations[121-123]. Dysregulated dopamine neuron firing will aberrantly signal that irrelevant stimuli are of importance, thereby imbuing percepts and thoughts with abnormal salience, in turn leading to inappropriate associations and causal attributions[124]. There are also mechanisms through which uncoordinated dopamine signalling may contribute not only to the generation of delusional beliefs, but also to the imperviously rigid form of delusional thought[123,125].

Recent work has attempted to identify more precisely the mechanisms through which dopaminergic dysfunction may contribute to symptoms. The experience of a stimulus depends not only on the sensory inputs resulting from that stimulus, but also on prior expectations regarding the probability of a percept. Auditory hallucinations appear to result from a stronger influence of prior expectations upon sensory percepts[126], and this increased weighting of priors has been associated with greater levels of amphetamine-induced dopamine release in the striatum[127].

In terms of understanding the development of delusions, a combined PET and MRI experiment found that dopamine release was related to neural signalling of belief updates rather than just sensory surprise[128]. This suggests that aberrant dopamine signalling may lead to irrelevant stimuli being understood as meaningful, the clinical relevance of which is supported by the finding that participants who displayed more aberrant belief updating showed greater subclinical paranoid ideation[128].

In addition to mesostriatal dopamine signalling, several cortical regions have also been implicated in salience processing[129,130]. The salience network comprises the anterior cingulate cortex and bilateral insula, and abnormalities of this network have been proposed as a core feature of schizophrenia pathophysiology[131]. The network has a key role in orchestrating dynamic switching between brain states, for example between a resting state and states associated with performing cognitively demanding tasks[132]. It is of relevance that dopamine signalling also plays a role in dynamic reorganization of brain states[133,134]. Recent work has demonstrated that mesostriatal dopamine signalling and salience network connectivity are tightly linked[135], although whether this relationship is disrupted in schizophrenia is not known.

Reward, motivation and negative symptoms

Reward and punishment are fundamental drivers of behaviour, and reinforcement learning models formalize the relationship between reward, states and behaviour. Prediction errors

allow the value of states and actions to be learnt, and are a key signal in many reinforcement learning models. Given the central role of dopamine in both coding prediction errors and in the cortical representation of environmental states, several studies have used this framework to explore the behavioural consequences of disrupted dopamine signalling[136].

Cortical D1 receptors play a central role in shaping the accurate neural representation of environmental states, by allowing precise inhibition of neural activity[137]. Reduced cortical dopamine signalling means that stimuli associated with reward cannot be accurately encoded, effectively foreclosing their ability to guide behaviour[137]. Furthermore, reduced cortical dopamine signalling may mean that reward-related representations are short-lived, with the consequence that, even if correctly represented, the motivational properties of reward-associated stimuli have a briefer impact[137].

Dopamine neurons fire in response to stimuli that have been previously associated with reward, and guide behaviour towards actions associated with previous reward[138]. A striatal hyperdopaminergic state may mean that reward-associated stimuli have reduced motivational influence, as aberrantly high background levels of dopamine signalling reduce the signal-to-noise ratio of adaptive phasic signalling[139]. This mechanism also has the potential to reduce the appetitive properties of a given reward, thereby reducing its impact to shape future behaviour, and accounting for negative symptoms such as anhedonia and amotivation[140-142]. This reduced signal-to-noise ratio may account for the reduced striatal activation to reward observed with fMRI in individuals with schizophrenia[51].

Cortical dopamine and cognitive symptoms

Cognitive symptoms of schizophrenia include deficits in working memory, executive function, and information processing. They occur prior to the onset of frank psychosis and account for a significant proportion of the morbidity associated with the illness[143-145].

The dorsolateral prefrontal cortex is central to many cognitive processes, and both functional and structural pathology of the region has been linked to the deficits seen in schizophrenia[146]. The molecular changes underlying cognitive symptoms, however, are unknown. Given the importance of D1 receptor signalling for cognition[147], reduced cortical dopamine signalling has long been hypothesized to contribute to the cognitive symptoms observed in schizophrenia. As discussed above, however, evidence regarding D1 receptors in schizophrenia is inconclusive, and there has been only a single study demonstrating reduced cortical dopamine release[95].

On the basis of preclinical work using a model of striatal D2 overexpression, it has also been proposed that excessive striatal dopamine signalling may lead to reductions in cortical dopamine and associated cognitive symptoms[7]. Therefore, it appears that both reduced and excessive dopamine signalling can have deleterious effects on cognition, which may contribute to the fact that there has been minimal success in developing dopamine modulating treatments for cognitive symptoms of schizophrenia[4,145].

GLUTAMATE

As reviewed above, there is significant evidence that dysfunction of the dopamine system is involved in the pathogenesis of schizophrenia. This may, however, occur downstream of other pathophysiological processes. Furthermore, schizophrenia is a heterogenous disorder, and dopaminergic dysfunction may not play a significant role in some individuals, while in others it may be only one of several pathological mechanisms.

Substantial evidence has accumulated implicating the glutamate system in the pathogenesis of schizophrenia. Glutamate is the major excitatory neurotransmitter in the central nervous system, and, in contrast to the anatomically localized cell bodies of dopamine neurons, glutamatergic neurons are widespread throughout the brain.

Glutamate receptors show considerable variety, and are classified as either ionotropic or metabotropic. Ionotropic receptors include the NMDA and the non-NMDA receptors – kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). NMDA and non-NMDA receptors are normally co-localized on neurons, and act synergistically in that the NMDA receptor has slower kinetics and tends to enhance depolarization initiated by non-NMDA receptors.

Following the discovery of the psychotomimetic effects of NMDA antagonists, the NMDA receptor has become a primary focus when considering potential glutamatergic dysfunction in schizophrenia. Below we examine the evidence associating schizophrenia with glutamatergic abnormalities, consider how these abnormalities may lead to symptoms, and review the potential of glutamate modulating agents as treatments.

Indirect evidence for glutamatergic dysfunction in schizophrenia

Animal models

The administration of NMDA antagonists to non-human primates and rodents has been shown to induce a variety of schizophrenia-like behaviours, such as sensorimotor gating impairments, increased locomotion, abnormal repetitive movements, and cognitive and social deficits[38]. NMDA antagonism has also been shown to lead to hippocampal hypermetabolism, similar to that which has been observed in schizophrenia[148,149].

A genetic animal model that reduced levels of the NMDA co-agonist D-serine was associated with neurobiological changes similar to those observed in schizophrenia, such as reduced dendritic spine density and hippocampal volume[39]. Several other genetic mice models, such as those involving inactivation of D-amino oxidase[40] and reduction of the synaptic protein dys-

bindin[41], also show NMDA receptor hypofunction accompanied by behavioural and neurobiological changes analogous to those observed in schizophrenia.

CSF and post-mortem studies

Initial small studies of CSF found reduced glutamate levels in patients, but these findings were not replicated[42,43]. However, CSF and post-mortem brain levels of kynurenic acid, an NMDA receptor antagonist, have consistently found to be raised, although not plasma levels[44].

Post-mortem studies investigating structural alterations of glutamate neurons have generally found reductions in dendrite arborization, spine density, and synaptophysin expression across frontal and temporal regions[45].

mRNA expression of specific glutamate receptors and their subunits has also been investigated across multiple brain regions. Although several studies have found reduced expression of NMDA receptor subunits such as GRIN1, GRIN2A and GRIN2C, these have not been consistently replicated across brain regions[45], although – when regions are examined individually – there is evidence of reduced GRIN1 expression in the hippocampus[45]. A recent study examining samples from over 500 individuals with schizophrenia found increased exon skipping in GRIN1, that would affect the extracellular ligand binding site[30]. Fewer studies have examined protein expression of these subunits, and these are also inconsistent in their findings[45].

There have also been a small number of studies investigating enzymes involved in glutamate metabolism. Excitatory amino acid transporters (EAAT) remove glutamate from the synaptic cleft. After reuptake from the synapse, glutamine synthetase converts glutamate to glutamine. When glutamine is delivered to neurons, it is converted back to glutamate by glutaminase. There is some preliminary evidence that both mRNA and protein levels of EAAT2, the transporter responsible for the majority of glutamate uptake, are reduced in frontal and temporal areas of patients with schizophrenia, while glutaminase mRNA levels and enzymatic activity have been found to be raised in two studies examining, respectively, the thalamus and dorsolateral prefrontal cortex[45].

Although the caveats regarding post-mortem studies discussed above remain, several of the findings covered here are consistent with impaired functioning of the NMDA receptor. In addition to the direct pathology suggested by the findings relating to GRIN1, the reduced expression of EAAT2 and the increased expression of glutaminase may be understood as compensatory responses attempting to increase synaptic glutamate levels.

Psychopharmacology of NMDA antagonists

The administration of NMDA receptor antagonists, such as phencyclidine and ketamine, to healthy controls has been repeatedly shown to induce manifestations similar to the positive, negative and cognitive symptoms of schizophrenia[46]. It has been demonstrated that NMDA receptor blockade by these compounds is both necessary and sufficient for their psychotomimetic effects[150].

These drugs have also been shown to exacerbate a similarly wide spectrum of symptoms in individuals with schizophrenia, in contrast to amphetamines, which predominantly worsen positive symptoms[151]. Furthermore, it has been shown that anti-NMDA receptor encephalitis may be associated with psychiatric presentations that resemble schizophrenia in some individuals[152]. NMDA antagonism has, therefore, been proposed to be a superior pharmacological model of schizophrenia, compared to amphetamines, given its ability to more reliably induce negative as well as positive symptoms[153,154].

Acute NMDA antagonist administration has typically been employed in experimental settings, since chronic administration to healthy controls cannot be ethically undertaken. However, chronic ketamine users show subthreshold psychotic symptoms across positive, negative and cognitive domains[47,48], and a subgroup of these chronic users develop a persisting psychosis that is more similar to schizophrenia than that induced by acute single dose ketamine administration[155].

Imaging glutamate in vivo

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) is the most frequently used technique for investigating the glutamate system in vivo. It does not require the use of ionizing radiation, and is significantly cheaper than PET.

^{1}H-MRS does, however, have several drawbacks, including the fact that it is unable to distinguish between intra- and extracellular compartments[156]. Glutamate does not act solely as a neurotransmitter, but is involved in protein synthesis and nitrogen metabolism, and is a precursor to GABA[157]. This means that it is not possible to infer whether differences between patients and controls relate to synaptic glutamate concentrations, as opposed to alterations in these other functions of glutamate. Even if one assumes that detectable abnormalities relate to differences in synaptic neurotransmission, it is not possible to determine whether this is secondary to differences in synaptic levels, as opposed to presynaptic dysfunction, or altered reuptake of glutamate.

At higher field strengths, glutamate and its metabolite glutamine can be distinguished, while at lower strengths the concentration of both, often abbreviated to Glx, is all that can be accurately quantified. Glutamine is synthesized from glutamate following the uptake of synaptic glutamate by astrocytes, and glutamine levels have been taken to be a marker of glutamate neurotransmission. However, as with glutamate, glutamine takes part in multiple cell process, which complicates interpretation[158].

There have been over fifty ^{1}H-MRS studies of the glutamate system in schizophrenia. A synthesis of their findings is complicated by methodological differences, notably in the imaging

sequences used, the brain regions studied, and the patient cohorts enrolled. Notwithstanding these issues, a meta-analysis of these studies has found several relatively consistent findings[159]. There is evidence that Glx (g=0.4) and glutamate (g=0.6) levels are raised in the basal ganglia, that glutamine concentration is increased in the thalamus (g=0.6), and that Glx levels are raised in the medial temporal lobe (g=0.3) in patients with schizophrenia (Table 2).

Although these effect sizes are in some instances comparable to those observed for presynaptic dopamine function, they represent considerably less studies. In the case of both glutamate in the basal ganglia and glutamine in the thalamus, only three studies have been performed, and as such these findings should be regarded as preliminary. The increased Glx levels observed in the medial temporal lobe represent 18 studies (13 in schizophrenia and 5 in clinical high-risk individuals).

If taken to reflect synaptic glutamate levels, the temporal lobe findings are consistent with the post-mortem findings discussed above, and the PET study discussed below, which suggest that receptor dysfunction is accompanied by compensatory changes that increase synaptic glutamate levels. This is also consistent with studies that have found hippocampal hyperactivity in psychosis, potentially resulting from dysfunction of NMDA receptors located on GABAergic interneurons[9,148,149].

In recent years, several studies have been performed using higher magnetic field strengths of up to 7 Tesla. Higher field strength has greater sensitivity, enabling greater separation of glutamate and glutamine peaks, and allowing for more accurate quantification. Two studies in first-episode patients have shown reduced glutamate concentrations in the anterior cingulate cortex[160,161], while another only found this in a subset of patients with predominantly negative symptoms[162]. No difference has been observed in several other investigations[163-166]. Overall this suggests that, even at high field strengths, group differences are inconsistent.

Another recent development is functional MRS. This involves acquiring multiple measures during a task or other stimulus, to investigate dynamic changes in metabolite measures. Changes in ^{1}H-MRS measures during a stimulus are proposed to result from compartmental shifts, as glutamate located extracellularly may contribute more to the signal. This results from the fact that, within presynaptic vesicles, metabolite movement is restricted, and therefore may have a faster T2 relaxation rate[167].

A study using a heat pain stress found a reduced anterior cingulate cortex glutamate response in individuals with schizophrenia compared to healthy controls[168], although interpretation is complicated by the fact that baseline glutamate levels were higher in patients. A similar pattern was seen in a study using a cognitive task in which patients showed reduced anterior cingulate glutamate response compared to controls[166].

Other neuroimaging techniques

Given the limitations of ^{1}H-MRS in determining the precise nature of glutamatergic abnormalities, several attempts have been made to develop radioligands capable of directly measuring glutamate receptors.

One study found reduced NMDA receptor binding in the left hippocampus of patients with schizophrenia, but no further studies have been attempted, in part due to concerns regarding a lack of specificity of the tracer. A recent study using a tracer for the metabotropic glutamate receptor 5 found no patient-control differences[169]. New tracers are under development, but lack of specificity remains an ongoing problem when attempting to image glutamate receptors[170].

^{13}C-MRS is another non-invasive imaging technique. It has lower sensitivity compared to ^{1}H-MRS, but, when combined with a ^{13}C labelled infusion, it has the potential to overcome some of the limitations associated with ^{1}H-MRS, specifically as regards to characterizing the glutamate-glutamine cycle[171]. This technique has been adopted to show that the majority of energy production in the brain supports glutamatergic activity and, although studies are yet to be performed in schizophrenia, it has recently been used in humans to show that ketamine increases glutamate-glutamine cycling[172,173].

Glutamate chemical exchange saturation transfer (GluCEST) is another novel technique for measuring glutamate in vivo. In addition to improved sensitivity, it allows for whole brain imaging without the need to specify a single voxel[174]. It has so far been used in a single investigation, which reported reduced glutamate levels in individuals with schizophrenia and those at clinical high risk, compared to healthy controls[175].

Glutamate across the psychosis spectrum

As with imaging of the dopamine system, efforts have been made to characterize glutamatergic function in individuals at clinical and genetic high risk for psychosis. Similarly, although a meta-analysis suggested that increased Glx levels might exist in the medial frontal cortex in individuals at clinical high risk of psychosis[165], recent studies have been negative[176-178], and there appear to be no clear differences between at-risk individuals and controls.

Given that ^{1}H-MRS measures of glutamate have been consistently shown to decline with age across the frontal cortex, anterior cingulate, hippocampus and basal ganglia[179-181], it may be that schizophrenia is associated with a distinct trajectory of change, and so differences only become detectable later in the time course of the illness.

Consequences of glutamatergic dysfunction

Unlike dopamine neurons, which are restricted to relatively well circumscribed anatomical pathways, glutamate signalling occurs ubiquitously throughout the brain and, as a result, dysfunction of this system has the potential to account for a wide range of impairments.

However, given the limitations regarding techniques for directly quantifying the glutamate system in vivo, there is a paucity of

direct evidence regarding the precise nature of glutamatergic dysfunction in schizophrenia, and studies looking at the relationship between ^{1}H-MRS measures of glutamate and symptom severity have produced inconsistent findings[182]. Indeed, both increased and decreased level of glutamate as measured by ^{1}H-MRS have been proposed to support a hypothesis of NMDA hypofunction in schizophrenia[183,184].

NMDA receptors, sparse coding and memory

NMDA receptors play a vital role in orchestrating several cognitive processes, including working memory[185]. One of the mechanisms involved in the efficient cortical representation of information is that of sparse coding.

Different cortical cell classes encode information differently. More superficial cell layers code "sparsely". This means that only a small proportion of cells within a region will be spiking, and information is thus encoded spatially[186]. This is in contrast to deeper layers, where the majority of cells may be firing, and information is encoded by variations in the rate of spiking[186]. Sparse coding involves great spatial precision in terms of the area of excitation, and this is mediated by strong lateral inhibition secondary to dense GABAergic interneuron networks within the superficial layers[187].

Sparse coding allows the maintenance of multiple mnemonic networks, and also the protection of encoded memories from distractors[137]. Disruption to sparse coding mechanisms has been shown to lead to the development of false memories in animal models[188]. Both individuals with schizophrenia and healthy controls administered NMDA antagonists display phenomena that may result from impaired sparse coding – a smaller working memory buffer, decreased mnemonic precision, and false alarms in working memory[137,189]. Decreased inhibition secondary to hypofunction of NMDA receptors on GABAergic interneurons could account for a disruption to the spatial precision of superficial layer firing, but this remains to be definitively tested.

Excitatory/inhibitory balance and neuronal oscillations

Synchronized neuronal oscillations are associated with a wide range of cognitive processes, such as working memory. These oscillations result from a tightly maintained balance between excitatory and inhibitory populations of neurons, and can be measured in vivo using electroencephalogram (EEG).

The balance between excitation and inhibition is crucial for normal physiological function, and NMDA receptors play a critical role here. Disruption to this balance has been proposed to result in the EEG abnormalities observed in schizophrenia. This disorder is associated with increased resting gamma oscillations, that have been linked to cognitive symptoms[190]. This disruption of normal oscillatory activity mirrors what has been observed with ketamine administration in healthy volunteers.

A range of molecular alterations have been proposed to potentially lead to excitatory/inhibitory imbalance in schizophrenia, including excessive pruning of dendritic spines, and intrinsic GABAergic abnormalities[191]. Another candidate mechanism is that of NMDA hypofunction. NMDA antagonists preferentially act on GABA interneurons, because these neurons have a more depolarized membrane potential. It has also been proposed that, in schizophrenia, NMDA hypofunction may preferentially affect interneurons[192], which would in turn lead to greater activity of pyramidal neurons. This uncoordinated increased activity may underlie disruptions to normal oscillatory activity mentioned above, and act as noise, impairing the ability of coordinated activity to be passed down to subcortical regions[150].

FACTORS UNDERLYING GLUTAMATERGIC AND DOPAMINERGIC DYSFUNCTION

Genetic factors

Over a hundred risk loci have been associated with schizophrenia by large scale genome-wide association studies (GWAS)[195]. Given the evidence implicating dopamine in the disorder, it is surprising that only one of the loci was found to be associated with the dopamine system, specifically the dopamine D2 receptor.

Analyses specifically looking at genes involved in dopamine synthesis, signalling and metabolism have also been unable to find a signal other than for D2 receptors, and this accounts for a negligible proportion of the overall genetic risk[196]. However, other loci strongly linked to schizophrenia, such as 10q24.32, have shown associations with dopamine synthesis capacity[197], as have polymorphisms of the gene DISC1[198]. Although relatively small sample sizes were used, these findings suggest that genetic factors related to schizophrenia may indirectly affect the dopamine system.

In the case of glutamate, many genes involved in the development and maintenance of glutamatergic synapses are not only implicated by loci significantly associated with schizophrenia in GWAS[193,195], but also by studies examining rarer genetic risk factors[199,200]. This includes genes that directly code for components of glutamate receptors, such as GRIN2A, GRIA1 and GRM3, and genes involved in facilitating glutamatergic neurotransmission through other means, such as that coding for serine racemase (SRR). These results provide some of the strongest support that disruption of glutamatergic signalling is a fundamental component of schizophrenia pathophysiology.

Induced pluripotent stem cells (iPSCs) allow for the generation of live neurons, in vitro, from somatic cells taken from patients. These neurons are best conceptualized as modelling fetal brain tissue, primarily reflecting an underlying genetic architecture, distilled from environmental exposures[201]. The use of iPSCs can be particularly valuable in elucidating the effects of genetics in a polygenic disorder such as schizophrenia, where disease risk is encoded by complex networks of genes, the functional consequences of which are not easily intuited.

Several studies using this technique have investigated how the dopamine system may be affected. One study found reduced DAT expression, indicating immaturity in dopaminergic neurons derived from individuals with schizophrenia[202]. Another study, however, found that dopamine neurons derived from patients

tended to develop more rapidly, and showed increased dopamine release[203]. Small sample sizes and differences in experimental protocols likely contributed to these discrepancies[204].

iPSCs have also been used to study the glutamate system in neurons derived from individuals with schizophrenia. Two studies have demonstrated deficits in glutamate receptor signalling in patient-derived cells[205,206], and a follow-up study identified specific gene modules associated with these deficits in glutamatergic signalling[201]. One investigation found reduced glutamate release in schizophrenia-derived cells differentiated to hippocampal dentate gyrus cells[207], while another found delayed maturation of both dopaminergic and glutamatergic neurons, and that glutamatergic neurons displayed a reduced ability to form synaptic contacts[202].

Environmental factors

Acute psychosocial stress has been shown to induce striatal dopamine release[208,209]. Measures of presynaptic dopamine function are raised in migrants, and those that have experienced childhood trauma, both of which are risk factors associated with schizophrenia[210-213]. However, another risk factor for schizophrenia, heavy cannabis use, is associated with blunted dopamine synthesis capacity and release[214,215].

Although acute stress has been shown to increase cortical glutamate level in preclinical models, this has not been demonstrated in humans using ^{1}H-MRS[216,217]. ^{1}H-MRS studies in cannabis users generally report reduced glutamate levels in both cortical and subcortical areas, which is in keeping with animal work[218]. Of note, a recent iPSC study showed that, in neurons derived from individuals with schizophrenia, tetrahydrocannabinol administration led to depressed glutamate signalling[219].

Neural circuits and dopamine-glutamate interactions

The evidence discussed above suggests that, while the dopamine hypothesis can account for the positive symptoms of psychosis, it is less clear whether it can fully account for negative and cognitive symptoms. Similarly, while glutamatergic models of psychosis are able to replicate a wide range of symptoms of psychosis, they do not directly account for the finding of increased presynaptic striatal dopamine function, nor the clinical effectiveness of dopamine antagonists. This suggests that dysfunction in both systems contributes to the pathophysiology of schizophrenia, and highlights the need to understand how these two systems may interact.

Much research has investigated dopamine-glutamate relationships in humans using pharmacological challenges. Amphetamine administration has been shown to increase cortical glutamate levels, as measured using ^{1}H-MRS[220], but dopamine antagonists do not have consistent effects on glutamate levels as measured using ^{1}H-MRS[221]. Several, but not all, PET studies have found that ketamine administration is associated with striatal dopamine release[222]. While glutamatergic dysfunction may encourage dopaminergic disinhibition, it is clear that this is not the only route to symptoms, given that dopamine antagonists do not entirely ameliorate the effects of NMDA antagonists[223].

Recent studies have combined PET and MRI measurements in the same individuals to investigate this relationship without the use of pharmacological modulation. One study in healthy individuals found that increased dopamine synthesis capacity in the ventral striatum was associated with both reduced cortical and increased striatal levels of glutamate[224]. This is in keeping with the imaging studies discussed above, in which both increased dopamine and glutamate measures were observed in the striatum in schizophrenia, which could potentially result from increased activity of glutamatergic projection to the striatum. Other studies found the same relationship between cortical glutamate and striatal dopamine in clinical high-risk and first-episode psychosis patients, but not in controls[225,226].

Theories linking glutamate and dopamine have proposed that defective NMDA receptors on cortical GABA interneurons result in inadequate inhibition of glutamatergic projections to the midbrain. This, in turn, may overstimulate mesostriatal dopamine neurons. In order to account for purported cortical dopamine deficits, it has also been proposed that overactive glutamatergic projections might overstimulate GABA interneurons in the ventral tegmental area, and thereby overinhibit mesocortical projection neurons[227].

The first of these proposed mechanisms has support from studies demonstrating ketamine-induced release of striatal dopamine. It is also in line with the ^{1}H-MRS studies discussed above, if the increased basal ganglia glutamate levels observed in schizophrenia are taken to represent increased activity of cortical projections. The second mechanism remains speculative[222].

It is likely, however, that the relationship between glutamate and dopamine is not one-way but bidirectional. As mentioned above, human studies have suggested that modulation of the dopamine system affects cortical glutamate levels. Preclinical studies have shown that mice genetically modified to have upregulated dopaminergic signalling display disrupted glutamatergic signalling of thalamocortical neurons[228]. Furthermore, cortical dopamine receptors have been shown to influence local glutamate release[229].

The wide range of pathways potentially linking the two systems, and the potential for opposing effects depending on the number of interneurons within a circuit, means that it is not possible to disentangle precise mechanisms with currently available neuroimaging methods.

TREATMENT

Dopamine modulating treatments

Antipsychotics are effective treatments for positive symptoms in the majority of patients with a diagnosis of schizophrenia. However, about one third of patients show persistent positive symptoms despite treatment, and this has been termed treatment-resistant schizophrenia[230].

Recent studies have suggested that dopamine synthesis capacity may predict which patients respond to treatment. An initial study found that dopamine synthesis capacity was only raised in those with a treatment-responsive illness[84], which is consistent with a more recent prospective study[231].

Even when effective in treating positive symptoms, dopamine antagonists do not typically show significant benefit for negative and cognitive symptoms. This is expected if these symptoms do not primarily relate to the hyperdopaminergic state, and particularly so if they result from deficits in dopaminergic signalling.

All currently licensed antipsychotics exert their dopaminergic effects primarily at postsynaptic D2 receptors, which is downstream of the presynaptic hyperdopaminergic state that has been observed in molecular imaging studies. There are currently a number of treatments in development which attempt to correct dysregulated dopamine function further upstream.

Apomorphine was shown to be an efficacious treatment in an early clinical trial[232]. Although later studies did not consistently replicate this finding[4], a recent investigation suggested that this drug may normalize dopaminergic activity, potentially via agonism of presynaptic autoreceptors[233]. Another upstream approach involves agonism of trace amine type 1 receptors. This has been shown preclinically to both reduce midbrain dopamine neuron activity, and reduce the locomotor response to amphetamine[234].

Finally, the PET studies discussed above have demonstrated that presynaptic dopaminergic dysfunction is greatest in the dorsal striatum[83], and muscarinic receptor 4 positive allosteric modulators specifically inhibit dorsal striatal dopamine release, with efficacy demonstrated in some clinical trials[235,236].

The dopamine system may also be more indirectly regulated via upstream circuits. The potential of glutamate signalling to modulate dopamine neurotransmission has been discussed above. Reduced functioning of GABAergic interneurons has also been suggested to contribute to disinhibition of dopamine neurons, and alpha 5 selective GABA agonists have been proposed as means of addressing this. Although neuroimaging and preclinical work provides conceptual support, efficacy in patients is yet to be demonstrated[4].

There is also the chance of intervening downstream of postsynaptic receptors. Stimulation of D2 receptors inhibits cyclic adenosine monophosphate (cAMP) production, while phosphodiesterase inhibitors have an opposing effect by preventing cAMP breakdown. Phosphodiesterase inhibitors may therefore have the potential to block the downstream effects of excessive D2 signalling, and also the potential benefit of boosting cortical D1 signalling[237]. Although clinical trials testing these compounds have not yet been successful[4], there is a significant variability in the regional expression of phosphodiesterase inhibitor subtypes, and those showing the greatest cortical expression remain to be tested[238].

Glutamate modulating treatments

Glutamate modulating treatments for schizophrenia fall into two camps: those that aim to augment NMDA signalling, and those that aim to reduce levels of synaptic glutamate proposed to be pathologically raised as a result of NMDA hypofunction. A general challenge for the development of glutamatergic treatments is that they will typically have relatively global effects, whereas pathology may be confined to discrete cell types such as NMDA receptors on specific GABAergic interneurons[239,240].

Since directly augmenting synaptic glutamate levels could have pathologically excitotoxic effects, efforts at augmenting NMDA signalling have focused on the receptor's glycine modulatory site. For activation of the NMDA receptor, glycine or D-serine has to bind to the glycine modulatory site on GluN1 subunit, in addition to glutamate binding at the GluN2 subunit. Agonists of the glycine modulatory site – including glycine, D-serine and D-cycloserine – have demonstrated the ability to attenuate the psychotogenic effects of NMDA antagonists in preclinical studies, although this has not been clearly demonstrated in humans [150].

A meta-analysis of clinical trials in individuals with schizophrenia suggested that D-serine may be effective in the treatment of negative symptoms[241], but a relatively large trial was subsequently negative[242]. The same meta-analysis also suggested that glycine may have a benefit for overall symptoms as well, but large scale trials are needed for clear confirmation of this effect[241]. A meta-analysis of glutamate positive modulators in the treatment of cognitive symptoms, including D-serine and glycine, did not demonstrate benefit over placebo[243].

Poor blood-brain barrier penetration by glycine and some of the other co-agonists means that occupancy of the glycine modulatory site may be insufficient to exert clinically measurable effects. To address this, an alternative approach has involved attempts to increase synaptic glycine levels by blocking the glycine type 1 transporter, thereby inhibiting removal of glycine from the synapse.

Bitopertin, a glycine type I transporter inhibitor, appeared to be a promising compound in this regard, showing good blood-brain barrier penetration, with encouraging results in early clinical trials[244]. However, later trials were not successful, perhaps due to the unusually high placebo responses, or the use of chronic patient populations, given that there is some evidence that intervention is likely to be more effective in early illness stages[245]. More recently, another glycine type I transporter inhibitor was shown to increase long-term potentiation (a marker of neuroplasticity) in individuals with schizophrenia, and the compound awaits testing in clinical trials[246].

Another potential approach may be to lower levels of kynurenic acid, which is an endogenous antagonist of the glycine modulatory site[247]. Cyclooxygenase-2 inhibitors reduce kynurenic acid levels, and celecoxib has shown benefit as an adjunctive treatment in early psychosis, but not chronic illness[248]. However, a recent in vitro study found that celecoxib did not significantly reduce kynurenic acid levels, while parecoxib and niflumic acid did[249]. So, it may be that other cyclooxygenase-2 inhibitors have the potential for greater efficacy.

Based on findings that NMDA antagonism increases synaptic glutamate levels, the second general approach has focused on

hypotheses that NMDA hypofunction may result in pathologically raised levels of glutamate, and therefore inhibiting the release of glutamate from terminals may be therapeutic[150,250].

The metabotropic glutamate 2 receptor (mGluR2) is located presynaptically on glutamate neurons, where it acts as an autoreceptor to regulate glutamate release[251]. Positive allosteric modulators of mGluR2 have been found to be effective in reducing the cognitive impairments induced by ketamine[252]. However, efficacy in clinical trials has not been consistently shown[253]. One complication in these trials was the high rate of placebo response.

Riluzole (2-amino-6-trifluormethoxy benzothiazole) has also been shown to reduce synaptic glutamate levels through a wide range of mechanisms, and an initial trial found it to be effective in treating negative symptoms in schizophrenia, potentially by altering striatocortical connectivity[254,255]. Similarly, lamotrigine inhibits glutamate release via inhibition of several ion channels, and attenuates the psychotomimetic effects of ketamine[256]. Lamotrigine has also shown efficacy as an adjunctive medication for clozapine-resistant schizophrenia, although studies to date are small and findings inconsistent[257].

Neuroimaging studies have suggested that treatment-resistant schizophrenia may not show the dopaminergic dysfunction seen in treatment-responsive schizophrenia[84,231,258], and that glutamatergic abnormalities may be of greater pathophysiological relevance in those cases of schizophrenia which do not respond to antipsychotic medications[259,260]. Supporting this view, there is evidence that cortical glutamate levels are higher in patients with treatment-resistant schizophrenia relative to responsive patients[261]. One of the reasons for unsuccessful clinical trials may therefore be that glutamate modulating treatments are only of significant benefit in a subgroup of patients.

OUTSTANDING QUESTIONS AND FUTURE DIRECTIONS

There are a number of outstanding issues when it comes to understanding the role of dopamine and glutamate in schizophrenia. In the case of glutamate, it is not possible to separate extra- and intracellular compartments using MRS, and we cannot accurately probe receptors and synaptic glutamate levels in vivo. As a result, it is not currently possible to precisely characterize the nature of glutamate dysfunction in schizophrenia. It remains unclear whether synaptic glutamate levels are abnormal, whether receptors are altered, and where any alterations might be localized within the brain.

Because of this, it is not clear whether treatments should aim to reduce synaptic glutamate levels or augment glutamatergic neurotransmission[150]. This likely contributes to the fact that to date no glutamate modulating agents exist that demonstrate unequivocal efficacy in schizophrenia.

There is a need for radioligands with reliable binding at the NMDA receptor to allow for investigation of receptor abnormalities in schizophrenia. PET ligands for other proteins involved in glutamatergic signalling, such as AMPA receptors, enzymes involved in glutamate synthesis and metabolism, and the kynurenine pathway, would also represent a considerable advance. In the meantime, other methods, such as functional MRS, ^{11}C-MRS, GluCEST and 7T ^{1}H-MRS, may advance our understanding by allowing more precise inferences regarding the nature of glutamatergic abnormalities in schizophrenia.

Imaging studies have provided more information when it comes to the dopamine system. However, several questions remain unanswered, such as the nature of cortical dopamine function in schizophrenia, whether a cortical hypodopaminergic state co-exists with the striatal hyperdopaminergic condition, and how dopaminergic dysfunction evolves across illness course.

The improved resolution of PET cameras has allowed for greater anatomical precision in identifying the locus of dopaminergic dysfunction in schizophrenia. Early hypotheses had suggested that this dysfunction might be characterized by aberrant mesolimbic function. However, the use of new PET cameras has demonstrated that the greatest patient-control differences are in the dorsal striatum[83]. The resolution of PET is still relatively coarse, however, and this limits the precision with which inferences can be made about which specific neuron groups are affected.

In addition to advances in hardware, further progress may be made by employing novel methods, such as super-resolution techniques, in which multiple low-resolution images are combined to create a high-resolution image, or deep learning methods, where anatomical information from an MRI scan is used to help improve the resolution of the PET image[262,263]. The limited resolution of in vivo imaging techniques means that it is difficult to directly test circuit level hypotheses regarding the nature of disrupted glutamate-dopamine interactions in schizophrenia. Instead, hypotheses regarding circuit interactions are largely based on preclinical, post-mortem and pharmacological studies, but await direct testing in patients.

Translation of research findings to clinically useful applications is not straightforward, and compounds acting though mechanisms other than dopamine receptor antagonism have not consistently shown efficacy in clinical trials. However, there exists a range of novel mechanisms for manipulation of both glutamate and dopamine signalling that show potential and await clinical testing. As discussed above, it may be that certain treatments are only of benefit in specific subgroups of patients, and clinical benefit may therefore be optimized by stratifying participants on the basis of underlying neurobiology[231,259]. Given the coarseness of current clinical measures[264], the development of imaging biomarkers to evaluate treatment effects at a neurobiological level may assist in moving the field forward[265].

The non-linearity inherent to neural signalling within a complex network means that, even if one disregards potential inconsistencies between studies, a coherent integration of existing findings is challenging. The combination of large datasets across illness phases, biophysical networks models to link molecular pathology to the macroscale dysfunction observed with neuroimaging, and carefully designed experiments to test and finesse

these models is one route to integrating what at times appears to be a disparate collection of findings[266,267].

CONCLUSIONS

The hypothesis that dopamine signalling is altered in schizophrenia is supported by animal studies, post-mortem research, and the clinical effects of drugs that either block or accentuate dopaminergic neurotransmission. In addition, over the past 25 years, substantial evidence has accumulated from PET studies that there is increased dopamine synthesis and release capacity in schizophrenia, that is greatest within the dorsal striatum.

Genetic findings do not provide strong support for the idea that dopaminergic dysregulation is a primary abnormality. Rather, it appears that the dopaminergic dysfunction is more likely to develop downstream of abnormalities in other systems, including the glutamatergic system. It also appears that environmental factors may play a significant role in the development of dopaminergic dysregulation. Dopamine antagonists remain the mainstay for pharmacological treatment of schizophrenia, but there is increasing evidence that these are not effective for all patients.

Evidence for glutamate playing a role in the pathophysiology of schizophrenia initially came from the psychotomimetic effects of NMDA antagonists. While preclinical and post-mortem findings are consistent with this hypothesis, there is limited support from imaging studies. However, in contrast to dopamine, recent genetic findings do provide support for the view that glutamatergic abnormalities may play a major role in schizophrenia pathophysiology. However, progress is hampered by the challenges involved in precisely characterizing the system in vivo, and, while a wide range of glutamate modulating agents have been investigated, none have clear clinical efficacy.

Despite the limitations described, as regards both treatment efficacy and direct evidence for dysfunction, the dopamine and glutamate hypotheses of schizophrenia remain influential and relevant. This is not least because, as recent data demonstrate, they possess the flexibility to accommodate new findings, and to provide ongoing potential avenues for the development of novel treatments.

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Gender competence and mental health promotion

Cultural competence is a familiar construct. It encompasses individual attitudes and behaviors, as well as organizational policies related to consideration of culture in practices and services. It reflects values about diversity and rights to equitable access to care, and the skills to enable people, agencies and systems to work effectively in culturally pluralist situations.

Gender competence is less familiar. It comprises the capacity to recognize gender-based discriminatory attitudes and behaviors; knowledge about gender-based policies and initiatives to improve equality of opportunities and outcomes; and actions to counter gender-based stereotypes in research, learning environments and clinical practice. Gender competence in health care promotes equity in health outcomes.

Stereotypes are qualities assigned to groups of people based on gender, ethnicity, nationality, sexual orientation or other traits. Gender-based stereotypes are fixed beliefs and attributions about characteristics, capabilities and behaviors based on a person's sex. They are always limiting, including of rights and entitlements. They reinforce disparities in privileges and power in private and public spheres of life, and influence day-to-day exchanges in relationships. They are automatic and can be embedded in a single word or descriptive phrase, and are harmful when used to predict, judge or understand human behavior[1].

Worldwide, women carry higher burdens of unpaid work and caregiving, and have disproportionate experiences of childhood maltreatment, and violence perpetrated by an intimate partner. They have less access to the protections of education, income-generating work and financial decision-making. These carry risks for their mental health across the life course[2].

Gender-based stereotypes are revealed in attitudes and beliefs about women's roles and responsibilities, including work, caregiving and income generation; and violent transgressions of their human rights, in clinical practice, research and public health initiatives.

There are principles about the management and prevention of occupational fatigue in workplaces in which there are long and irregular hours, including shift work. These prescribe maximum safe working hours, required nights of consecutive rest to recover from nightshifts, and intervals for sleep between shifts. However, because of gender stereotypes, there are no workplace safety requirements about occupational fatigue when the home is the workplace, and the work is caring for an infant.

Smith and Ellwood[3] assessed time spent on caregiving and available for sleep among mothers of three-month-old infants, using an electronic recording device. On average, there were 49 feeds, each lasting about 75 min, and 70 other occasions of carrying/holding/soothing the infant, for about 18 min each time, a total of more than 82 hours caregiving work per week. Mothers' sleep was in 18 different episodes, each lasting about 3 hours. The experiences are worse if the baby cries inconsolably and wakes frequently. Among women admitted consecutively to a residential early parenting centre for assistance with their unsettled babies, 80% had on average less than 6/24 hours sleep in the prior week, and 91% met criteria for clinically significant fatigue[4].

The usual ways in which clinicians enquire about these experiences include: Are you working?; When are you giving up work?; When are you going back to work?; Does he help you? Researchers classify women as not working or as working outside the home[5]. This reveals stereotypes that the endeavour of caring for an infant is not work, is not socially valued and is a female obligation with which men help. Women incorporate these pervasive stereotypes, reflected in the common responses that "I don't work" or "I am only a mother".

Prevalence varies among countries, but violence against women and girls is a universal phenomenon. Violent transgressions of the human rights of females begin prior to birth and occur across the life course in domestic, institutional and community settings. They encompass, but are not limited to, female feticide, sexual abuse of girls, female genital mutilation, dowry-related violence, sexual harassment and intimidation at work, trafficking, and violence perpetrated by an intimate partner. Women who are Indigenous or members of ethnic or religious minority groups, occupying low socio-economic positions, or refugees or asylum-seekers, are especially vulnerable[6]. Experiencing or witnessing interpersonal violence, especially when it occurs within households, is always harmful to mental health. The World Health Organization considers violence to be the principal gender-related cause of mental health problems among women[7].

For most of the 20th century, violence against women received scant research attention or recognition by clinicians and policy-makers. The first epidemiological surveys of perinatal mental health problems among women were published in the 1960s. Difficulties in the relationship with an intimate partner were more prevalent among the group with than without mental health problems, but this was conceptualized as women being depressed, having difficulties in their biological role and regarding their husbands as unhelpful and unsympathetic[8].

The first systematic review of the evidence about the relationship between intimate partner violence and perinatal mental health problems was published in 2013. Violence experienced during pregnancy was associated with a near five-fold increase in antenatal (odds ratio, OR=5, 95% CI: 4.04-6.17) and postnatal (OR=4.36, 95% CI: 2.93-6.48) depression[9]. Most countries, including well-resourced high-income nations, were unable to contribute data to this review because none were available.

Despite this evidence, the predominant theme in the contemporary literature is that women's mental health problems are biologically caused and have adverse effects on their partners, children and families. The alternative interpretation that their mental health problems might be a consequence of their environmental exposures remains rare[5].

Gender-informed approaches to mental health promotion require specific acknowledgement of gender-based risks. These

are underpinned by frank recognition of gender stereotypes and how these influence the ways in which research is conceptualized and designed, and data are collected and interpreted, as well as the language that is used in clinical encounters and recommendations in health promotion initiatives.

Gender competence requires explicit and intentional consideration of past experiences and current predicaments within their social and cultural contexts. Gender competence therefore seeks to comprehend and address experiences of discrimination, interpersonal violence and being devalued, and to counter internalized beliefs about roles, rights and responsibilities. Researchers, clinicians and public health professionals who advocate for these strategies and implement these approaches can be powerful agents of social change.

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Engagement of ethnic minorities in mental health care

Disparities in mental health care for ethnic minorities represent a serious public health concern, but one that could be at least partially remediated. Here we briefly describe lessons learned about how to engage these clients in the clinical encounter, particularly when social identities are not shared between client and clinician, which can lead to unease or distrust.

Lessons are intended to augment initiation in care, prevent premature termination of treatment, and offer patient-centered practices. We acknowledge that these recommendations could potentially apply to all clients, but propose that they may be especially beneficial for engaging ethnic minority groups, for whom social and economic disadvantage may amplify differences in social identity between client and clinician.

Multiple studies find that ethnic minorities are less likely to initiate, continue or complete mental health and substance use treatments, or adhere to recommended regimens[1,2]. Clients' disengagement from treatment may be partly due to the absence of clinician training to help bridge social identities when these are discordant in terms of perceived social position.

Social position, in this context, is defined as ethnic, economic or political hierarchy that clients and clinicians each systematically experience based on their objective characteristics (e.g., age, gender, education, income and occupation) and perceptions of how others value, accept and/or rank them.

Perceived social position differentials between client and clinician could augment prejudice and bias and decrease emotion recognition when the clinician is not able to appreciate the perspective of the client[3]. Therefore, our first lesson is to utilize strategies to overcome positional hierarchies associated with unjustified group attributions, pre-made assumptions, and imbalanced relational power characterizing client-clinician interaction[4].

Shared decision making in the clinical encounter rebalances power and encourages a collaborative dialogue between clinician and client[5], one where the client brings expertise of his/her illness and the clinician brings expertise of diagnosis and treatment. Shared decision making includes negotiations toward a shared agenda for the session ("What would be helpful for us to talk about?"), client involvement in decisions about treatment, and discussions about treatment options and recommendations[6].

The main approach to achieving true shared decision making is coaching clinicians to encourage the client's self-efficacy, reflect on the client's expressed choices, and help him/her weigh the pros and cons of his/her options. The clinician-client dynamic changes from one of clinician as director to assistant or facilitator. We urge clinicians to use collaborative language ("we", "us", "let's work this problem together", "we could try this") and to avoid verbal dominance (i.e., when clinician or client gives a monologue rather than sharing an equal dialogue) to convey a shared responsibility and power in the relationship.

When discussing treatment decisions or interpretations of behaviors or events, clinicians should recognize that presenting their opinions with certainty or relaying factual medical assertions can disempower clients. Therefore, clinicians should express their ideas with humility ("Maybe another way could be…"; "I don't know if I am right about this, but another possibility…"). This allows clients to accept, reject or modify the clinician's ideas while the clinician is receptive to the client's perspective.

Our second lesson is to center treatment goals on what is important to the client, based on his/her expressed concerns[7] ("How do you understand your problem?", "What does this problem represent to you?" "What do you think is causing this problem?"). In trials with ethnic minority populations, we begin every session by asking clients what they want to focus on, so that the content of the session, including exercises and skill building, is

tailored to the clients' immediate concerns.

Using a client's language in framing the problem aids both clinician and client in experiencing the problem through the client's eyes. For example, when a client states that he feels disgust for himself when using drugs, the clinician reminds him that he has previously stated that drugs help him feel confident and stable, and reframes his use of drugs as a potentially unhealthy coping tool when dealing with difficult circumstances.

In pediatric mental health practices, one mistake that can impede focus on the client's concerns is concentrating on generational hierarchies, or only asking the parents about what they see as the problem, bypassing the child's perspective. Clinicians should address children directly and ask about their concerns. This approach seeks to share a common view of the problem, directed by the client's experience.

Our third lesson for clinicians is to be willing to explain to clients who they are, share with clients some of their social identity, and ask clients to do the same. During a clinical encounter, for example, the clinician can share something he/she enjoys doing or dreamed about when moving to the US. In turn, the clinician may ask the client questions to magnify the importance of the client's social identity ("Do you want talk about your tattoos and what they represent, as you previously commented?").

These exchanges can facilitate learning about the clients' cultural, interpersonal or social worldview and attempted coping mechanisms that can shed light on how they comprehend their problems and what might be acceptable solutions. These strategies may also help clinicians avoid attribution errors and build trust based on a joint understanding of what words, behaviors or actions might mean.

We acknowledge that barriers to engagement in mental health care for minority populations, as well as for the clinician who treats them, may be attitudinal or structural in nature. These are barriers that require substantial cognitive efforts by clinicians to overcome and that require longer visits in resource poor environments where most of these populations are served. Some attitudinal barriers that interfere with engagement are stigma, bias, prejudice, and racial/ethnic discrimination[1,2,8].

Some structural barriers that might also influence engagement include linguistic obstacles in communicating, limited availability of times for care, and poor quality of services[1,2,8]. Furthermore, individual factors (e.g., socioeconomic status, self-efficacy, health literacy), organizational factors (e.g., policies and practices), and societal factors (e.g., social and community norms) interact to influence engagement in services[9]. Efforts to improve engagement in mental health care need to address both attitudinal and structural barriers.

Clinicians can adopt these engagement recommendations in their individual practices, but systemic changes are needed to solidify these strategies in mental health care settings. Systemic changes include incorporating engagement activities into clinician training and treatment protocols, offering flexible service delivery modes (e.g., by phone or within non-clinical settings), and integrating mental health care management to address social determinants of health.

Engaging ethnic minority clients requires clinicians to construct the clinical encounter with egalitarian collaboration that addresses the clients' needs, empowers their decision making, and amplifies their voice in treatment.

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Leveraging collaborative care to improve access to mental health care on a global scale

In most parts of the world, there are not enough mental health professionals to meet the demand. Psychiatrists, with critical expertise in treating patients with severe mental illness, diagnosing complex multimorbidity, and prescribing medications, are in particularly short supply. As with many other health-related inequities, this shortage is disproportionally pronounced in lower-income, rural and poorly resourced settings. To put the problem into perspective, high-income countries have more than 100 times as many psychiatrists as low-income countries[1].

Growing awareness of the global unmet need for mental health services has led to a number of efforts to extend the "reach" of psychiatrists by fostering partnerships with other health care professionals, mostly in primary care. There is a rich history of the implementation and evaluation of such models, which are often collectively termed "mental health integration", "behavioral health integration" or simply "integrated care".

Some strategies for integration focus on coordination and communication between psychiatrists and primary care providers (coordinated care), while others physically co-locate the two professions in the same space (co-located care). Still other models emphasize population-health principles, and include systematic

communication and coordination between a team of providers working in concert to address all of the health care needs of each patient (fully integrated care).

One such model, collaborative care, leverages task-sharing and the services of a team of providers to deliver person-centered, evidence-based treatment of common mental health problems, such as depression and anxiety, in primary care settings.

Specifically, collaborative care utilizes a trained behavioral health care manager to conduct assessments, collect data with common screening instruments such as the Patient Health Questionnaire-9 (PHQ-9), and provide evidence-based brief psychological interventions, such as motivational interviewing, behavioral activation, or problem-solving treatment. Care managers also support the longitudinal management of psychiatric medications prescribed by primary care providers, with guidance from a designated psychiatric consultant, who may be located on-site or elsewhere and connect via telehealth technologies.

In evidence-based collaborative care programs, clinical outcomes are tracked using an electronic registry, and care managers keep in regular contact with patients to make sure that nobody falls through the cracks. During regular case-review sessions, the psychiatric consultant and the care manager review the entire patient caseload, focusing on those who present diagnostic challenges or are not improving with treatment as expected. Psychiatric consultants make diagnostic and treatment recommendations to the care manager, who works with the patient's primary care providers to implement these recommendations. Patients who are not improving may be referred for an in-person or virtual psychiatric evaluation, or to additional specialty mental health, medical or social services as clinically indicated. The collaborative care team communicates with the primary care provider on a regular basis, to provide updates on treatment progress and to make adjustments to the treatment plan as needed.

Although originally studied for depression in primary care[2], collaborative care has since been evaluated in more than 80 randomized controlled trials (mostly in the US and other high-income countries) for a variety of common mental health problems[3,4], and the vast majority of studies have shown that it is superior to usual care.

According to the Advancing Integrated Mental Health Solutions (AIMS) Center at the University of Washington, evidence-based collaborative care includes five core principles: patient-centered team care, population-based care, measurement-based treatment to target, evidence-based care, and accountable care[5]. In addition to their application in well-controlled experimental settings, collaborative care programs that follow these core principles have been successfully adopted in numerous settings worldwide, including lower-income countries and locations with little access to on-site mental health specialists[6].

Although the collaborative care model is highly effective and robust to different health care environments, it is not without challenges related to implementation and sustainability. Like other health services interventions that are first studied in well-resourced and highly controlled settings, it can experience a substantial "voltage drop" when implemented in real-world settings without close attention to fidelity or the core principles outlined above.

A growing body of literature has focused specifically on the application of collaborative care in low- and middle-income countries, and recent reports have highlighted a number of barriers, such as the lack of technological resources or reliable sources of electricity, insufficient government or health system coordination, mental health stigma, a scarcity of skilled workers, inadequate buy-in from local leaders, a lack of access to medications, and financing challenges[7,8]. Successful implementation of collaborative care requires an organized primary care system, which is able not only to address acute medical problems, but also to provide ongoing care for chronic or recurrent health problems.

Difficulties notwithstanding, collaborative care remains one of the best studied and most effective approaches to improving access to mental health care around the globe. Several recent studies have identified strategies to overcome common implementation and sustainability barriers, such as mobilizing and leveraging existing community resources, engaging with global advocates, and framing mental health integration as a pathway to improving the health care system at large[8].

Several studies have demonstrated the feasibility of providing population-based mental health care using these models in low- and middle-income countries, including the Programme for Improving Mental Health Care (PRIME) and the Emerging Mental Health Systems in Low- and Middle-Income Countries (EMERALD) in parts of Africa and Asia[9].

In summary, collaborative care is an extensively evidence-based model for the treatment of common mental health problems in diverse primary care settings. With dire psychiatrist shortages globally, there is growing interest in ways to "leverage" scarce resources and bring mental health expertise to the places where it is most needed. Although the majority of studies of collaborative care to date have been conducted in high-income countries, an emerging body of literature suggests that common barriers can be overcome and that this approach can be successfully adapted and operationalized in lower-resource settings.

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The role of new technologies in monitoring the evolution of psychopathology and providing measurement-based care in young people

Two of the most important innovations in clinical psychiatry over the last decade have been the deployment of youth-focused early intervention services and the development of a clinical staging framework for clinical care and pathophysiological research[1,2]. Together, they engage young people in active clinical care, promote secondary prevention strategies and provide the platform for more detailed clinical research.

These developments respond directly to the epidemiology, namely, that most mood and psychotic syndromes have their onset in adolescence and are associated with social and educational impairment and other at-risk behaviors (notably suicidal thoughts and behaviors, and alcohol and other substance misuse)[3].

Critics of these proactive innovations highlight possible adverse effects, including premature assignment of specific diagnoses, unwarranted exposure to medicines and inappropriate deployment of specialized health resources. The true value of these developments can only be determined by detailed longitudinal assessment of the relevant clinical, social and occupational outcomes[4]. For the individuals most affected, and their families and carers, this means a commitment by service organizations to serious long-term partnerships in which the relevant data are collected.

To conduct meaningful analyses, we need detailed data tracking over the 5-15 year period after onset (i.e., from adolescence to age 30 years). We also require linking of data from multiple informants (individuals, family members and carers, clinicians, as well as health care and related social, educational and employment-based organizations).

Data collection methods demand highly personalized and flexible approaches, so that the maximum data is collected not only at key points of biological or social transition, but also when a young person is exposed to a major new risk factor, experiences a major deterioration or receives an effective intervention.

Previously, such responsive longitudinal research, and innovative clinical practice, relied largely on cohort studies confined to highly specialized clinical centres. Additionally, these studies required large investments in trained research staff, but typically resulted in only a limited number of data entry points over the course of illness. These traditional methods struggle to provide sufficient data for the type of modelling exercises that are now required to describe the many possible trajectories that are possible during this key developmental period[5].

So, in the 21st century, is it possible to improve the quality of such fundamental health services[4,6] and conduct such essential clinical and linked pathophysiological research at scale? As we now have the digital technology tools, the answer can be "yes"[6]. That is, it is possible to access the digital infrastructure, combined with security and privacy systems and ethical frameworks, to conduct both enhanced clinical care and longer-term research.

Personal digital technologies can regularly collect both subjective and objective data from young people, include complementary information from families and carers, and be linked to smart health information systems. We have demonstrated that, when these tools are co-designed with young people, and implemented in genuine ethically-based partnerships, they have the capacity for extensive uptake in relevant population groups[6].

In our own clinical work, we have emphasized the power of such technology-based approaches to track multiple dimensions (i.e., illness type, stage and course; social and occupational function; suicidal thoughts and behaviors; physical health; alcohol and other substance use) concurrently[4]. Linking clinical tracking to mobile personal technologies which collect additional objective data adds depth to these approaches[7,8].

So, for the first time, we can track – in real time, in great detail and at scale – emerging psychopathology in young people. The populations of great interest can include those seeking health care, as well as those who are "at risk" (due to exposure to known genetic, familial or environmental risk factors). The changing patterns of relevant symptoms, syndrome clusters, linked behaviors (e.g., alcohol or substance use; self-harm or suicidal behaviors) or physiological markers (e.g., 24-hour patterns of motor activity) can be directly followed[8]. These patterns in "at-risk" or already unwell cohorts can then be compared with normal youth who are passing through this same developmental period.

The data derived from such endeavors present major opportunities to move beyond those simplistic or diagnostically-siloed approaches that have characterized many previous clinically-oriented cohort or broad population studies. When combined with other powerful design strategies (i.e., genetic, longitudinal twin, family, clinical intervention or concurrent neurobiological assessment studies), as well as new data analytic approaches[5], it is likely that we will be able to move beyond our current broad descriptive efforts and delineate much clearer paths to the onset and course of major mood and psychotic syndromes.

In our systems, this personal data acquisition process (and any subsequent transfer to a third party or consolidation within any other deidentified data set) is controlled by the young person. However, with appropriate permissions, it can also be embedded within smart health systems. This has the real advantage of providing the technical basis for genuine and real-time measurement-based care. When each new care decision is made collaboratively, and on the basis of shared and highly personalized data, the potential to improve long-term clinical and functional outcomes may be realized. Additionally, ongoing youth participation in such data acquisition exercises is greatly enhanced

when we focus, first, on the provision of optimal care and, second, on deepening our understanding of these complex illness trajectories.

These activities cannot only be conducted at scale, but can also be implemented in a wide variety of settings. Importantly, digital technologies are not simply a luxury tool of affluent youth in developed countries. As telecommunication infrastructure is now an essential component of economic and social development in many economies, they are rapidly becoming an everyday part of life in most regions of the world. As recognized by the World Economic Forum[9], as long as the major ethical, equity and privacy challenges are addressed, they are the tools most likely to bring effective mental health care not only to young people during the period of peak onset of mental ill-health, but also more rapidly to the world's eight billion people.

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The pursuit of euthymia

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Psychiatrists often consider the positive characteristics displayed by a patient in their clinical judgment, yet current assessment and treatment strategies are shifted on the side of psychological dysfunction. Euthymia is a transdiagnostic construct referring to the presence of positive affects and psychological well-being, i.e., balance and integration of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings for shaping future accordingly (consistency), and resistance to stress (resilience and tolerance to anxiety or frustration). There is increasing evidence that the evaluation of euthymia and its components has major clinical implications. Specific instruments (clinical interviews and questionnaires) may be included in a clinimetric assessment strategy encompassing macro-analysis and staging. The pursuit of euthymia cannot be conceived as a therapeutic intervention for specific mental disorders, but as a transdiagnostic strategy to be incorporated in an individualized therapeutic plan. A number of psychotherapeutic techniques aiming to enhance positive affects and psychological well-being (such as well-being therapy, mindfulness-based cognitive therapy, and acceptance and commitment therapy) have been developed and validated in randomized controlled clinical trials. The findings indicate that flourishing and resilience can be promoted by specific interventions leading to a positive evaluation of one's self, a sense of continuing growth and development, the belief that life is purposeful and meaningful, satisfaction with one's relations with others, the capacity to manage effectively one's life, and a sense of self-determination.

Key words: Euthymia, psychological well-being, resilience, mental health, clinimetrics, positive psychology, well-being therapy, mindfulness-based cognitive therapy, acceptance and commitment therapy

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About sixty years ago, M. Jahoda published an extraordinary book on positive mental health[1]. She denied that "the concept of mental health can be usefully defined by identifying it with the absence of a disease. It would seem, consequently, to be more fruitful to tackle the concept of mental health in its more positive connotation, noting, however, that the absence of disease may constitute a necessary, but not sufficient, criterion for mental health."[1]

She outlined criteria for positive mental health: autonomy (regulation of behavior from within), environmental mastery, satisfactory interactions with other people and the milieu, the individual's style and degree of growth, development or self-actualization, and the attitudes of an individual toward his/her own self (self-perception/acceptance). The book indicated that mental health research was dramatically weighted on the side of psychological dysfunction[1].

It took a long time before such imbalance started being corrected, as a result of several converging developments that occurred in the late 1990s.

First, C. Ryff[2] introduced a method for the assessment of Jahoda's psychological dimensions based on the self-rating Psychological Well-Being (PWB) scales. This questionnaire disclosed that ill-being (e.g., major depressive disorder) and well-being were independent although interrelated dimensions[3,4]. This means that some individuals might have high levels of both ill-being and well-being, while others might have major mental disorders and poor psychological well-being, and further individuals might have no major mental disorders and high levels of psychological well-being.

Further, the naive conceptualization of well-being and distress as mutually exclusive (i.e., well-being is lack of distress and should result from removal of distress) was challenged by clinical research. Patients with a variety of mental disorders who were judged to have remitted on symptomatic grounds still presented with impairment in psychological well-being compared to healthy control subjects[5,6].

Second, impairments in psychological well-being were found to be a substantial risk factor for the onset and recurrence of mental disorders, such as depression[7,8]. Psychological well-being thus needs to be incorporated in the definition of recovery[9]. There has been growing recognition that interventions that bring the person out of negative functioning may not involve a full recovery, but the achievement of a neutral position[9]. Jahoda[1] had postulated that a full recovery can be reached only through interventions which facilitate progress toward restoration or enhancement of psychological well-being.

A third converging development occurred as the concept of positive mental health became the target of an increasing amount of research[10]. Its domains were very broad, such as the presence of multiple human strengths (rather than the absence of weaknesses), including maturity, dominance of positive emotions, subjective well-being, and resilience[10].

Yet, probably the strongest input to the consideration of psychological well-being came from the positive psychology movement initiated by the American Psychological Association in the year 2000[11], which had a huge impact on psychology and the society in general in a very short time. The movement can be credited with delivering the message that psychology needs to consider the positive as well as the negative, an issue that was much later extended to psychiatry[12]. Yet, this movement attracted considerable criticism[13,14]. Positive psychology developed outside the clinical field and, not surprisingly, its oversimplified approach (happiness and optimism, the more the better) was likely to clash with the complexities of clinical reality[13,14].

Despite these developments, consideration of psychological well-being has had a limited impact so far on general practice. The aim of this review is to illustrate that clinical attention to psychological well-being requires an integrative framework, which may be subsumed under the concept of euthymia[15], as well as specific assessment and treatment strategies. Such an approach may unravel innovative and promising prospects both in clinical and preventive settings.

EUTHYMIA AS AN INTEGRATIVE FRAMEWORK

In 1991, Garamoni et al[16] suggested that healthy functioning is characterized by an optimal balance of positive and negative cognitions and affects, and that psychopathology is marked by deviations from this balance. Treatment of psychiatric symptoms may induce improvement of well-being, and, indeed, scales describing well-being were found to be more sensitive to medication effects than those describing symptoms[17]. In turn, changes in well-being may affect the intensity of symptomatology[18,19].

Excessively elevated levels of positive emotions can also become detrimental[13], and are more connected with mental disorders and impaired functioning than with psychological well-being.

Optimal balanced well-being can be different from person to person, according to factors such as personality traits, social roles, cultural and social context. Table 1 outlines the bipolar nature of Jahoda-Ryff's dimensions[20]. Appraisal of positive cognitions and affects thus needs to occur in the setting of an integrative framework, which may be provided by the concept of euthymia.

This term has a Greek origin and results from the combination of *eu*, well, and *thymos*, soul. The latter element, however, encompasses four different meanings: life energy; feelings and passions; will, desire and inclination; thought and intelligence. Interestingly, the corresponding verb (*euthymeo*) means both "I am happy, in good spirits" and "I make other people happy", "I reassure and encourage".

The definition of euthymia is generally ascribed to Democritus: one is satisfied with what is present and available, taking little heed of people who are envied and admired and observing the lives of those who suffer and yet endure[21]. It is a state of quiet satisfaction, a balance of emotions that defeats fears.

The Latin philosopher Seneca translated the Greek term euthymia by *tranquillitas animi* (a state of internal calm and contentment) and linked it to psychological well-being as a learning process. Happiness is not everything, and what is required is *felicitatis intellectus*, the awareness of well-being. Plutarch, who attempted a synthesis of Greek and Latin

Table 1 The spectrum of dimensions of psychological well-being

IMPAIRED LEVEL	BALANCED LEVEL	EXCESSIVE LEVEL
Environmental mastery		
The person feels difficulties in managing everyday affairs; he/she feels unable to improve things around; he/she is unaware of opportunities.	The person has a sense of competence in managing the environment; he/she makes good use of surrounding opportunities; he/she is able to choose what is more suitable to personal needs.	The person is looking for difficult situations to be handled; he/she is unable to savoring positive emotions and leisure time; he/she is too engaged in work or family activities.
Personal growth		
The person has a sense of being stuck; he/she lacks sense of improvement over time; he/she feels bored and uninterested in life.	The person has a sense of continued development; he/she sees one's self as growing and improving; he/she is open to new experiences.	The person is unable to elaborate past negative experiences; he/she cultivates illusions that clash with reality; he/she sets unrealistic standards and goals.
Purpose in life		
The person lacks a sense of meaning in life; he/she has few goals or aims and lacks sense of direction.	The person has goals in life and feels there is meaning to present and past life.	The person has unrealistic expectations and hopes; he/she is constantly dissatisfied with performance and is unable to recognize failures.
Autonomy		
The person is over-concerned with the expectations and evaluations of others; he/she relies on judgment of others to make important decisions.	The person is independent; he/she is able to resist to social pressures; he/she regulates behavior and self by personal standards.	The person is unable to get along with other people, to work in team, to learn from others; he/she is unable to ask for advice or help.
Self-acceptance		
The person feels dissatisfied with one's self; he/she is disappointed with what has occurred in past life; he/she wishes to be different.	The person accepts his/her good and bad qualities and feels positive about past life.	The person has difficulties in admitting his/her own mistakes; he/she attributes all problems to others' faults.
Positive relations with others		
The person has few close, trusting relationships with others; he/she finds difficult to be open.	The person has trusting relationships with others; he/she is concerned about welfare of others; he/she understands give and take of human relationships.	The person sacrifices his/her needs and well-being for those of others; low self-esteem and sense of worthlessness induce excessive readiness to forgive.

cultures, criticized the concept of euthymia involving detachment from current events, as portrayed by Epicurus, and underscored the learning potential of mood alterations and adverse life situations.

In the psychiatric literature, the term euthymia essentially connotes the lack of significant distress. When a patient, in the longitudinal course of mood disturbances, no longer meets the threshold for a disorder such as depression or mania, as assessed by diagnostic criteria or by cut-off points on rating scales, he/she is often labelled as euthymic. Patients with bipolar disorder spend about half of their time in depression, mania or mixed states[22]. The remaining periods are defined as euthymic[23-27]. However, considerable fluctuations in psychological distress were recorded in studies with longitudinal designs, suggesting that the illness is still active in those latter periods, even though its intensity may vary[28]. It is thus questionable whether subthreshold symptomatic periods truly represent euthymia[28].

Similar considerations apply to the use of the term euthymia in unipolar depression and dysthymia. Again, euthymia is often defined essentially in negative terms[29], as a lack of a certain intensity of mood symptoms, and not as the presence of specific positive features that characterize recovery[9].

Jahoda[1] outlined a characteristic that is very much related to the concept of euthymia. She defined it as integration: the individual's balance of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings for shaping future accordingly (consistency), and resistance to stress (resilience and tolerance to anxiety or frustration). It is not simply a generic (and clinically useless) effort of avoiding excesses and extremes. It is how the individual adjusts the psychological dimensions of well-being to changing needs.

In the past decades, there has been an increasing interest in the concepts of flexibility and resilience portrayed by Jahoda[1]. Psychological flexibility has been viewed[30] as the ability to: recognize and adapt to various situational demands; change one's paradigms when these strategies compromise personal or social functioning; maintain balance among important life domains; display consistency in one's behavior and deeply held values. The absence of flexibility is linked to depression, anxiety and the general tendency to experience negative emotions more frequently, intensely and readily, for longer periods of time, in what has been subsumed under the rubric of neuroticism[30].

Resilience has been defined as the capacity to maintain or recover high well-being in the face of life adversity[31]. Looking for the presence of wellness following adversity involves a more demanding and rigorous conception of resilience than the absence of illness or negative behavioral outcomes, the usual gold standards. Examples are provided by life histories of persons regaining high well-being following depression, or the ability to sustain psychological well-being during serious or chronic illness. Resilience is thus conceptualized as a longitudinal and dynamic process, which is related to the concept of flourishing. Issues such as leading a meaningful and purposeful life as well as having quality ties to others affect the physiological substrates of health[32]. The concept of subjective incompetence (a feeling of being trapped or blocked because of a sense of inability to plan or start actions toward goals) stands as opposite to that of resilience[33]. Individuals who perceive themselves as incompetent are uncertain and indecisive as to their directions and aims.

Fava and Bech[15] defined a state of euthymia as characterized by the following features (Figure 1):

- Lack of mood disturbances that can be subsumed under diagnostic rubrics. If the subject has a prior history of mood disorder, he/she should be in full remission. If sadness, anxiety or irritable mood are experienced, they tend to be short-lived, related to specific situations, and do not significantly affect everyday life.
- The subject has positive affects, i.e., feels cheerful, calm, active, interested

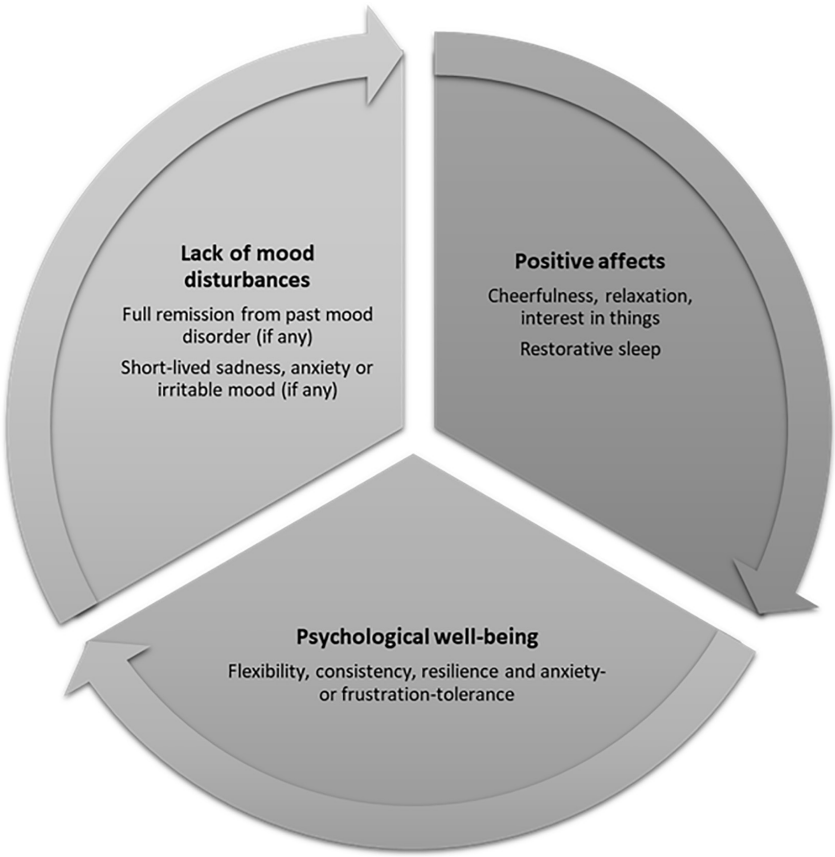

Figure 1 The concept of euthymia

in things, and sleep is refreshing or restorative.
- The subject manifests psychological well-being, i.e., displays balance and integration of psychic forces (flexibility), a unifying outlook on life which guides actions and feelings for shaping future accordingly (consistency), and resistance to stress (resilience and tolerance to anxiety or frustration).

This definition of euthymia, because of its intertwining with mood stability, is substantially different from the concept of eudaimonic well-being, that has become increasingly popular in positive psychology[34]. Indeed, research on psychological well-being can be summarized[35] as falling in two general groups: the hedonic viewpoint focuses on subjective well-being, happiness, pain avoidance and life satisfaction, whereas the eudaimonic viewpoint, as portrayed by Aristotle, focuses on meaning and self-realization and defines well-being in terms of degree to which a person is fully functioning or as a set of wellness variables such as self-actualization and vitality. However, the two viewpoints are inextricably linked in clinical situations, where they also interact with mood fluctuations[14]. The eudaimonic perspective ignores the complex balance of positive and negative affects in psychological disturbances[13,16].

Whether an individual meets the criteria of euthymia or not, it is important to evaluate its components in clinical practice and to incorporate them in the psychiatric examination. There is, in fact, extensive evidence that positive affects and well-being represent protective factors for health and increase resistance to stressful life situations[6,32,36-38].

CLINICAL ASSESSMENT OF POSITIVE AFFECTS AND PSYCHOLOGICAL WELL-BEING

Clinical assessment is aimed to exploring the presence of positive affects and psychological well-being, as well as their interactions with the course and characteristics of symptomatology. In order to analyze these characteristics in an integrative way, we need a clinimetric perspective[39-41]. The term "clinimetrics" indicates a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include the types, severity and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems in functional capacity; reasons for medical decisions (e.g., treatment choices), and many other aspects of daily life, such as well-being and distress[39-43].

Positive affects

While there have been considerable efforts to quantify and qualify psychological distress[44], much less has been done about assessing positive affects such as feeling cheerful, calm, active, interested in things, friendly[45,46].

Self-rating scales and questionnaires have been the preferred method of evaluation, and there are several instruments available[45,46]. Two instruments stand out for their clinimetric properties: the World Health Organization-5 Well-Being Index (WHO-5)[47] and the Symptom Questionnaire (SQ)[17].

The WHO-5 scale consists of five items that cover a basic life perception of a dynamic state of well-being. Such items have been incorporated in the Euthymia Scale[15], that has been found to entail clinimetric validity and reliability[48]. The Symptom Questionnaire is a self-rating scale with 24 items referring to relaxation, contentment, physical well-being and friendliness, and 68 items referring to anxiety, depression, somatization and hostility-irritability[17]. Extensive clinical research has documented its sensitivity to change and ability to discriminate between different populations[45].

In their clinical practice, psychiatrists weigh positive affects to evaluate the overall severity and the characteristics of a disorder. For instance, in order to discriminate depression from sadness, psychiatrists look for instances of emotional well-being that interrupt depressed mood and for reactivity to environmental factors. Indeed, the DSM-5 requires the presence of depressed mood most of the day, nearly every day, for the diagnosis of major depression. Psychiatrists also weigh the intensity of positive emotions and their borders with elation and behavioral activation to determine the bipolar characteristics of a mood disorder. However, current formal assessment strategies fail to capture most of this information[49]. Table 2 outlines the Clinical Interview for Euthymia (CIE), that covers such missing areas. The first five items explore the contents of positive affects, as depicted by the WHO-5[47].

Psychological well-being

There are several instruments to assess psychological well-being states and dimensions[45,46].

The PWB scales have been used extensively in clinical settings[6]. They encompass 84 items and six dimensions (environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others)[2]. The questionnaire, because of its length, may be problematic to use in a busy clinical setting. A shorter version, the 6-item part of the PsychoSocial Index[50,51], has been developed and submitted to clinimetric validation: it was found to be a sensitive measure of well-being, yet it does not allow differentiation of the various dimensions. A structured interview based on the PWB scales[2] has also been devised[14].

A 10-item self-rating scale, the Acceptance and Action Questionnaire (AAQ-II), is available to measure psychological flexibility[52,53]. Yet, flexibility is only one component of euthymia.

Further, both the PWB scales and derived indices and the AAQ-II provide assessment of the impaired and optimal levels, but do not yield information about excessive levels. Such information is included in the CIE (Table 2). Items 6 to 17 of the interview assess both polarities of psychological well-being dimensions developed by Jahoda[1] and measured by the PWB scales[2]. The interview also allows to collect information about flexibility, resilience and consistency (items 18 to 22).

Table 2 The Clinical Interview for Euthymia (CIE)

POSITIVE AFFECTS

1. Do you generally feel cheerful and in good spirits? YES NO
2. Do you generally feel calm and relaxed? YES NO
3. Do you generally feel active and vigorous? YES NO
4. Is your daily life filled with things that interest you? YES NO
5. Do you wake up feeling fresh and rested? YES NO

DIMENSIONS OF PSYCHOLOGICAL WELL-BEING

Environmental mastery

6. In general, do you feel that you are in charge of the situation in which you live? YES NO
7. Are you always looking for difficult situations and challenges? YES NO

Personal growth

8. Do you have the sense that you have developed and matured a lot as a person over the years? YES NO
9. Do you often fail to understand how things go wrong and/or set standards that you are unable to reach? YES NO

Purpose in life

10. Do you enjoy making plans for the future and working to make them a reality? In doing this, do you get a sense of direction in your life? YES NO
11. Are you constantly dissatisfied with your performance? YES NO

Autonomy

12. Is it more important for you to stand alone on your own principles than to fit in with others? YES NO
13. Are you able to ask for advice or help if needed? YES NO

Self-acceptance

14. In general, do you feel confident and positive about yourself? YES NO
15. Do you have difficulties in admitting your own mistakes, and/or attribute all problems to other people? YES NO

Positive relations with others

16. Do you have many people who want to listen when you need to talk and share your concerns, that is, do you feel that you get a lot out of your friendships? YES NO
17. Do you tend to sacrifice your needs and well-being to those of others? YES NO

FLEXIBILITY AND CONSISTENCY

18. If you become sad, anxious or angry, is it for a short time? YES NO
19. Do you keep on thinking of negative experiences? YES NO
20. Are you able to adapt to changing situations? YES NO
21. Do you try to be consistent in your attitudes and behaviors? YES NO
22. Are you able to handle stress most of the times? YES NO

Integration with psychiatric symptomatology

In most instances of diagnostic reasoning in psychiatry, the process ends with the identification of a disorder, according to a diagnostic system. Such a diagnosis (e.g., major depressive disorder), however, encompasses a wide range of manifestations, comorbidity, severity, prognosis and responses to treatment[54]. The exclusive reliance on diagnostic criteria does not reflect the complex situations that are encountered in clinical practice[54]. It needs to be integrated with positive affects and psychological well-being, as well as with a broad range of further elements, including stress, lifestyle, subclinical symptoms, illness behavior and social support, in a longitudinal perspective[54].

This approach is in line with the traditional psychopathological assessment, as outlined by M. Roth[55]: "looking before and after" into the lives of patients, considering the "stressful life circumstances that have surrounded the onset of illness, the premorbid personality and its Achilles heels, the historical record of the patient's development, adjustment in childhood, the relationship with parents, sexual life within and out of marriage, his achievements and ambitions, his interpersonal relationships, his adaptation in various roles and the strength or brittleness of his self-esteem"[55].

Two technical steps may facilitate the integration of the assessments of psychological well-being and distress.

The first technical step involves the clinimetric use of macro-analysis[42,54,56]. This method starts from the assumption that in most cases of mental disorders there are functional relationships with other more or less clearly defined problem areas, and that the targets of treatment may vary during the course of disturbances. For instance, let us consider the case of a woman with a recurrent major depressive disorder whose current episode has only partially remitted (see Figure 2). Clinical interviewing focused on symptoms may disclose the presence of residual symptoms (e.g., sadness, diminished interest in things, guilt, irritability), problems in the family (e.g., interpersonal frictions with her mother, recurrent thoughts regarding the loss of her father two years before) and unsatisfactory interpersonal relationships (e.g., repeated failures in romantic relationships). Clinical interviewing focused on euthymia may disclose low levels of autonomy (e.g., lack of assertiveness in many situations) and personal growth (e.g., strong feelings of dissatisfaction with her life and a sense of stagnation), and low self-acceptance (e.g., dissatisfaction with herself). As depicted in Figure 2, macro-analysis helps to identify the main problem areas in this specific situation.

Macro-analysis can be supplemented by micro-analysis, which may consist of dimensional measurements, such as observer- or self-rating scales to assess positive affects and psychological well-being[42,54,56]. The choice of these instruments is dictated by the clinimetric concept of incremental validity[54]: each aspect of psychological measurement should deliver a unique increase in information in order to qualify for inclusion.

The second technical step requires reference to the staging method, whereby a disorder is characterized according to severity, extension and longitudinal development[57,58]. The clinical meaning linked to the presence of dimensions of psychological well-being varies according to the stage of development of a disorder, whether prodromal, acute, residual or chronic[54]. Further, certain psychotherapeutic strategies can be deferred to a residual stage of psychiatric illness, when state-dependent learning has been improved by the use of medications[59]. The planning of treatment thus requires determination of the symptomatic target of the first line approach (e.g., pharmacotherapy), and tentative identification of other areas of concern to be addressed by subsequent treatment (e.g., psychotherapy)[59].

PSYCHOTHERAPEUTIC TECHNIQUES

Every successful psychotherapy, regardless of its target, is likely to improve subjective well-being and to reduce symptomatic distress[60]. Many psychotherapeutic techniques aimed to increase psychological well-being have been developed, although only a few have been tested in clinical settings[61-63].

A specific psychotherapeutic strategy has been developed according to Jahoda's concept of euthymia[1]. Well-being therapy (WBT) is a manualized, short-term psychotherapeutic strategy that emphasizes self-observation, with the use of a structured diary, homework and interaction between patient and therapist[14,20,64]. It can be differentiated from positive psychology

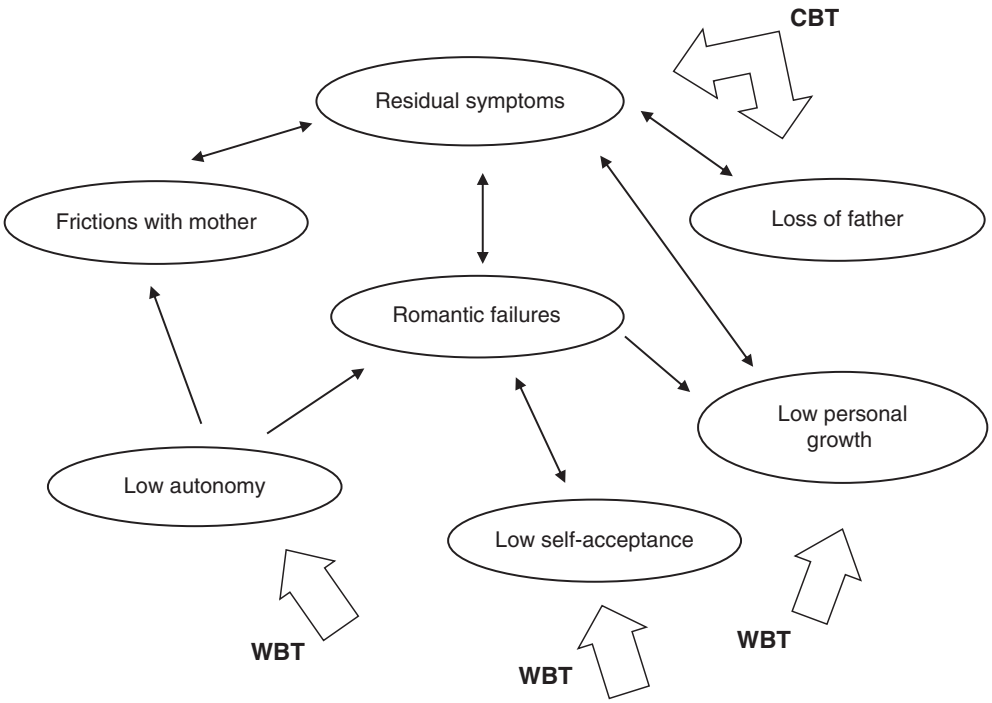

Figure 2 Macro-analysis of a partially remitted patient with recurrent major depressive disorder with therapeutic targets. CBT – cognitive behavior therapy, WBT – well-being therapy

interventions[62] on the basis of the following features: a) patients are encouraged to identify episodes of well-being and to set them into a situational context; b) once the instances of well-being are properly recognized, the patient is encouraged to identify thoughts and beliefs leading to premature interruption of well-being (automatic thoughts), as is performed in cognitive behavior therapy (CBT) but focusing on well-being rather than distress; c) the therapist may also reinforce and encourage activities that are likely to elicit well-being; d) the monitoring of the course of episodes of well-being allows the therapist to identify specific impairments or excessive levels in well-being dimensions according to Jahoda's conceptual framework[1]; e) patients are not simply encouraged to pursue the highest possible levels of psychological well-being in all dimensions, as is the case in most positive psychology interventions, but also to achieve a balanced functioning[15].

Another psychotherapeutic strategy intended to increase psychological well-being is mindfulness-based cognitive therapy (MBCT)[65], which is built on the Buddhist philosophy of a good life. Its main aim is to reduce the impact of potentially distressing thoughts and feelings, but it also introduces techniques such as mindful, non-judgmental attention and mastery, and pleasure tasks that may be geared to a good life[66]. However, the good life that is strived for is a state involving detachment, as portrayed by Epicurus, and not necessarily euthymia, as depicted by Plutarch.

Acceptance and commitment therapy (ACT)[67] is aimed to increase psychological flexibility[53]. It consists of an integration of behavioral theories of change with mindfulness and acceptance strategies. Unlike WBT, ACT argues that attempts at changing thoughts can be counterproductive, and encourages instead awareness and acceptance through mindfulness practice.

There are also further psychotherapeutic approaches, such as Padesky and Mooney's strengths-based CBT[68] and forgiveness therapy[69], that have been suggested to increase well-being, but await adequate clinical validation[66].

APPLICATIONS

The pursuit of euthymia in a clinical setting cannot be conceived as a therapy for specific mental disorders, but as a trans-diagnostic strategy to be incorporated in a therapeutic plan. Psychotherapeutic interventions aimed at psychological well-being are not suitable for application as a first line treatment of an acute psychiatric disorder[20,64]. However, most patients seen in clinical practice have complex and chronic disorders[54]. It is simply wishful thinking to believe that one course of treatment will be sufficient for yielding lasting and satisfactory remission. The use of psychotherapeutic strategies aimed at euthymia should thus follow clinical reasoning and case formulation facilitated by the use of macro-analysis and staging.

The treatment plan should be filtered by clinical judgment taking into consideration a number of clinical variables, such as the characteristics and severity of the psychiatric episode, co-occurring symptomatology and problems (not necessarily syndromes), medical comorbidities, patient's history, and levels of psychological well-being[54]. Such information should be placed among other therapeutic ingredients, and will need to be integrated with patient's preferences[70].

In the following sections, we illustrate a number of applications of strategies for enhancing and/or modulating psychological well-being. All these indications should be seen as tentative since, even when efficacy is supported by randomized controlled trials, the specific role of strategies modulating well-being in determining the outcome cannot be elucidated with certainty, because they are incorporated within more traditional approaches and a dismantling analysis is rarely implemented.

Relapse prevention

In 1994, a randomized controlled trial introduced the sequential design in depression[71]. Depressed patients who had responded to pharmacotherapy were randomly assigned to CBT or to clinical management, while antidepressant medications were tapered and discontinued. This design was subsequently used in a number of randomized controlled trials and was found to entail significant benefits in a meta-analysis[72].

The sequential model is an intensive, two-stage approach, where one type of treatment (psychotherapy) is applied to improve symptoms which another type of treatment (pharmacotherapy) was unable to affect. The rationale for this approach is to use psychotherapeutic strategies when they are most likely to make a unique and separate contribution to patient's well-being and to achieve a more pervasive recovery by addressing residual symptomatology. The sequential design is different from maintenance strategies for prolonging clinical responses obtained by therapies in the acute episodes, as well as from augmentation or switching strategies addressing lack of response to the first line of treatment[71,72].

Three independent randomized controlled trials using the sequential combination of cognitive therapy and WBT were performed in Italy[73,74], Germany[75] and the US[76]. In other trials that took place in Canada[77] and the Netherlands[78], some principles of WBT were used in addition to standard cognitive therapy. Further, there have been several investigations[79-87] in which MCBT was applied to the residual stage of depression after pharmacotherapy.

From the available studies, we are unable to detect whether the pursuit of psychological well-being was a specific effective ingredient and what was the mechanism decreasing the likelihood of relapse. Nonetheless, the clinical results that have been obtained are impressive, and the sequential model seems to be a strategy that has enduring effects in the prevention of the vexing problem of relapse in depression. It is conceivable, and yet to be tested, that similar strategies may involve significant advantages in terms of relapse rates also in other psychiatric disorders.

Increasing the level of recovery

The studies that used a sequential design clearly indicated that the level of remission obtained by successful pharmacotherapy

could be increased by a subsequent psychotherapeutic treatment[72]. Clinicians and researchers in clinical psychiatry often confound response to treatment with full recovery[9]. A full recovery can be reached only through interventions which facilitate progress toward restoration or enhancement of psychological well-being[1].

In a randomized controlled trial, patients with mood or anxiety disorders who had been successfully treated by behavioral (anxiety disorders) or pharmacological (mood disorders) methods were assigned to either WBT or CBT for residual symptoms[18]. Both WBT and CBT were associated with a significant reduction of those symptoms, but a significant advantage of WBT over CBT was detected by observer-rated methods. WBT was associated also with a significant increase in PWB scores, particularly in the personal growth scale[18].

A dismantling study in generalized anxiety disorder[19] suggested that an increased level of recovery could indeed be obtained with the addition of WBT to CBT. Patients were randomly assigned to eight sessions of CBT, or to CBT followed by four sessions of WBT. Both treatments were associated with a significant reduction of anxiety. However, significant advantages of the CBT/WBT sequential combination over CBT were observed, both in terms of symptom reduction and psychological well-being improvement[19].

While the clinical benefits of WBT in increasing the level of recovery have been documented in depression[64] and generalized anxiety disorder[19], this appears to be a possible target for a number of other mental health problems. Indeed, the issue of personal growth is attracting increasing interest in psychoses[88], and a role for WBT in improving functional outcomes as an additional ingredient to CBT in psychotic disorders has been postulated[89].

Modulating mood

WBT has been applied in cyclothymic disorder[90], a condition that involves mild or moderate fluctuations of mood, thoughts and behavior without meeting formal diagnostic criteria for either major depressive disorder or mania.

Patients with cyclothymic disorder were randomly assigned to the sequential combination of CBT and WBT or clinical management. At post-treatment, significant differences were found in outcome measures, with greater improvements in the CBT/WBT group. Therapeutic gains were maintained at 1- and 2- year follow-up.

The results thus indicated that WBT may address both polarities of mood swings and is geared to a state of euthymia[15]. Can the target of euthymia decrease vulnerability to relapse in bipolar spectrum disorders[91]? This is an important area that deserves specific studies.

Treatment resistance

A considerable number of patients fail to respond to appropriate pharmacotherapy and/or psychotherapy[54]. In a randomized controlled trial, MBCT was compared to treatment-as-usual (TAU) in treatment-resistant depression[92]. MBCT was significantly more efficacious than TAU in reducing depression severity, but not the number of cases who remitted.

A subsequent study[93] investigated the effectiveness of MBCT + TAU versus TAU only for chronic, treatment-resistant depressed patients who had not improved during not only previous pharmacotherapy but also psychological treatment (i.e., CBT or interpersonal psychotherapy). At post-treatment, MBCT + TAU had significant beneficial effects in terms of remission rates, quality of life, mindfulness skills, and self-compassion, even though the intent to treat (ITT) analysis did not reveal a significant reduction in depressive symptoms.

A number of case reports have suggested that WBT may provide a viable alternative when standard cognitive techniques based on monitoring distress do not yield any improvement or even cause symptomatic worsening in depression, panic disorder, or anorexia nervosa[64]. These data are insufficient to postulate a role for psychotherapies enhancing or modulating psychological well-being in these patient populations, yet this approach may yield new insights into this area.

Suicidal behavior

The relationship between future-directed thinking (prospection) and suicidality has been recently analyzed[94], and a potential innovative role for well-being enhancing psychotherapies has been postulated. Working on dimensions such as purpose in life may counteract suicidal behavior. Indeed, positive mental health was found to moderate the association between suicidal ideation and suicide attempts[95].

An issue that is not sufficiently appreciated is also the experience of mental pain that many suicidal patients may present. ACT was found to significantly reduce suicidal ideation as well as mental pain compared to relaxation in adult suicidal patients[96].

Discontinuing psychotropic drugs

Psychotropic drug treatment, particularly when it is protracted in time, may cause various forms of dependence[97]. Withdrawal symptoms do not necessarily wane after drug discontinuation and may build into persistent post-withdrawal disorders[98]. These symptoms may constitute a iatrogenic comorbidity that affects the course of illness and the response to subsequent treatments[97].

Discontinuation of antidepressant medications such as selective serotonin reuptake inhibitors, duloxetine and venlafaxine represents a major clinical challenge[99,100]. A protocol based on the sequential combination of CBT and WBT in post-withdrawal disorders has been devised[101] and tested in case reports[102].

Post-traumatic stress disorder

There has been growing awareness of the fact that traumatic experiences can also give rise to positive developments, subsumed under the rubric of post-traumatic growth[103]. Positive changes can be observed in self-concept (e.g., new evaluation of one's strength and resilience), appreciation of life opportunities, social relations, hierarchy of values and priorities, spiritual growth.

Well-being enhancing strategies may be uniquely suited for facilitating the process of post-traumatic growth. Two cases have been reported on the use of WBT, alone or in sequential combination with exposure, for overcoming post-traumatic stress disorder, with the central trauma being discussed only in the initial history-taking session[104].

Improving medical outcomes

The need to include consideration of psychosocial factors (functioning in daily life, quality of life, illness behavior) has emerged as a crucial component of patient care in chronic medical diseases[37]. These aspects also extend to family caregivers of chronically ill patients and health providers[36]. There has also been recent interest in the relationship between psychological flexibility and chronic pain[105]. It is thus possible to postulate a role for psychotherapeutic interventions modulating psychological well-being in the setting of medical diseases, to counteract the limitations and challenges induced by illness experience. The process of rehabilitation, in fact, requires the promotion of well-being and changes in lifestyle as primary targets of intervention[106].

In recent years, there has been increasing evidence suggesting that stressful conditions may elicit a pattern of conserved transcriptional response to adversity (CTRA), in which there is an increased expression of pro-inflammatory genes and a concurrent decreased expression of type 1 interferon innate antiviral response and IgG antibody synthesis[107]. Such patterns have been implicated in the pathophysiology of cancer[108] and cardiovascular diseases[109]. Frederickson et al[110] reported that individuals with high psychological well-being presented reduced CTRA gene expression, which introduces a potential protective role for psychological well-being in a number of medical disorders.

Improving health attitudes and behavior

Unhealthy lifestyle (e.g., smoking, physical inactivity, excessive eating) is a major risk factor for many of the most prevalent medical and psychiatric diseases[36,111]. Lifestyle modification focused on weight reduction, increased physical activity, and dietary change is recommended as first line therapy in a number of disorders, yet psychological distress and low levels of well-being are commonly observed among patients with chronic conditions and represent important obstacles to behavioral change[36].

It has been argued that enduring lifestyle changes can only be achieved with a personalized approach that targets psychological well-being[112]. As a result, strategies pointing to euthymia need to be tested in lifestyle interventions and in the prevention of mental and physical disorders.

CONCLUSIONS

Customary clinical taxonomy and evaluation do not include psychological well-being, which may demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same diagnosis. A number of psychotherapeutic strategies aimed to increase positive affects and psychological well-being have been developed. WBT, MBCT and ACT have been found effective in randomized controlled clinical trials.

An important characteristic of WBT is having euthymia as a specific target. This perspective is different from interventions that are labelled as positive but are actually distress oriented. An additional novel area in psychotherapy research can ensue from exploring euthymia as a characteristic of successful psychotherapists, as the Greek verb equivalent implies.

The evidence supporting the clinical value of the pursuit of euthymia is still limited. However, the insights gained may unravel innovative approaches to the assessment and treatment of mental disorders, with particular reference to decreasing vulnerability to relapse, increasing the level of recovery, and modulating mood.

These fascinating developments should be welcome by all those who are disillusioned with the current long-term outcomes of mental disorders. These outcomes may be unsatisfactory not because technical interventions are missing, but because our conceptual models, shifted on the side of psychological dysfunction, are inadequate.

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Constructing a liberated and modern mind: six pathways from pathology to euthymia

Traditional psychiatric nosology has been largely based on the idea that human psychological suffering reflects a latent disease[1]. As Fava and Guidi note in their paper[2], this conception has interfered with a more balanced and positive approach. It is not just that the focus on psychological distress has overwhelmed needed attention to positive experience. It is also that the latent disease model underlying syndromal diagnoses provides minimal clinical guidance regarding the nature of psychological health. It is obvious that human thriving is not merely the absence of distress. However, without a more adequate approach, clinicians are not given guidance about how to pivot their attention from pathology toward psychological prosperity in a more meaningful and coherent way.

If a process-based diagnostic approach is adopted, however, clear pathways arise from pathology to euthymia. More so than eudaimonic detachment, euthymia denotes the balanced satisfaction of human needs and yearnings. Just as distressing human emotions reflect the frustration of core yearnings, positive human emotions and well-being reflect their accomplishment. For that reason, we may be able to use the core human yearnings reflected inside pathological processes to provide a kind of roadmap for the creating of euthymia itself.

In an extended evolutionary approach to process-based diagnosis, processes of change link to variation, selection, retention, and context sensitivity in at least six psychological dimensions: affect, cognition, attention, self, motivation, and overt behavior[3]. As a set, these psychological dimensions are then nested in between social/cultural and genetic/physiological levels of analysis.

The psychological flexibility model (PFM) that underlies acceptance and commitment therapy (ACT) contains six known pathological processes of change that are paired with six known positive processes of psychological growth[4,5]. These six pairs line up with the six dimensions just listed.

In the area of affect, the negative change process of experiential avoidance pairs with the positive process of experiential acceptance; in the cognitive area, cognitive fusion and entanglement pairs with cognitive defusion; in attentional areas, rigid attention to the past and future, via rumination and worry, pairs with flexible, fluid and voluntary attention to the now; in the area of self, defense of a conceptualized self is paired with a perspective taking sense of self and ongoing self-awareness; in the motivational area, unhealthy forms of compliance, self-gratification, or aversive and avoidant rule-based demands are paired with chosen values; in the overt behavioral area, perfectionism, impulsivity or procrastination are paired with committed and step-by-step acquisition of broader patterns of values-based action.

What is not usually noticed in these pairings inside the PFM is that they are connected by deep human yearnings[6]. Consider those focused on by self-determination theory, one of the best empirically supported approaches to human needs: belonging, autonomy and competence[7]. Entanglement with a conceptualized self can be thought of as the mental mismanagement of a yearning to belong, in which people attempt to gain group membership and social connection or support by presentation of a persona that is especially able or especially needy. Over time, the mental attachment to specialness undermines belonging by fostering narcissistic pretense and avoidant/self-aggrandizing forms of "self-esteem", or coercive presentations of pathos. Either of these forms of adjustment lowers healthy connection and eventually drives others away. Perspective taking and shared awareness, conversely, are known to foster genuine connection, attachment and belonging.

In a similar way, the yearning for autonomy or self-directed meaning is mismanaged by compliance, self-gratification and rule-based demands, but is satisfied by chosen values; while the yearning for competence is mismanaged by perfectionism, impulsivity or procrastination but is satisfied by the committed construction of larger and larger patterns of values-based action.

In all of these pairs, the deep yearning underneath pathological processes of change is not the problem – pathology is just the wrong solution to the correct human challenge. What draws people into pathology is the one-two punch of short-term and more certain contingencies dominating over longer-term and more probabilistic ones, and an excessive reliance on the evolutionarily recent adaptation of symbolic thinking and problem solving.

Those general features are managed in ACT by the three remaining pairs of change processes in the PFM. By learning cognitive defusion skills, the yearning for understanding and coherence, that becomes increasingly central as symbolic language is acquired, can be met in a more generally useful way. Instead of trying to achieve literal coherence, in which all thoughts line up neatly in a coherent and consistent row, the person learns to step back from symbolic thinking processes and allow them to impact life choices based on functional coherence – the wise understanding that comes from allowing useful thoughts to guide behavior based on their history of workability over the longer term, while respectfully declining the mind's invitation to comply with the rest.

Similarly, instead of trying to satisfy an inborn yearning to feel by always "feeling good" – that is, by feeling only those events that are cognitively evaluated as "good" or "desirable" (which ultimately leads to a reduced capacity to feel at all) – a more defused approach is taken to those evaluations, allowing emotions to be explored and felt more openly and without needless defense. These acceptance skills satisfy the yearning to feel, and allow the helpful knowledge that emotions contain to be used, leading to more capacity for joy, appreciation, love, and well-being. Finally, the yearning to be oriented can focus less on

the ruminated past or mentally constructed future, and more on a deeper connection with what is actually present, inside and out.

Pathological change processes can thus be thought of as mismanaged yearnings. This mismanagement is caused by an evolutionary mismatch between half a billion-year-old learning processes or even more ancient genetic, epigenetic, perceptual, sensory and neurobiological systems, and the dominance of symbolic reasoning and problem solving that is 200 to a thousand times more recent, but that has been put on steroids in the modern technological era[8]. By focusing on what lies beneath pathology, however, a roadmap to euthymia is revealed.

The flexibility, consistency and resilience that define euthymia are fostered by healthy management of yearnings for belonging, coherence, feeling, orientation, self-directed meaning, and competence, in turn fostering wise psychological management of social/cultural and physical/biological health challenges. From the viewpoint of processes of change, psychopathology itself contains much the same lesson in its evidence for sources of mismanagement of these very same yearnings and challenges.

Flexibility is based in part on the increased and conscious context sensitivity afforded by perspective taking and voluntary attentional control; consistency is fostered by the greater motivational dominance of values, and the acquisition of committed action skills; resilience is fostered by greater emotional and cognitive openness and their ability to incorporate both "negative" and "positive" experiences into a life worth living. Considered as a set, these PFM skills foster euthymia, because they allow us to do a better job of evolving on purpose, supported by healthy psychosocial forms of variation, selection, retention, and context sensitivity.

People in distress are not broken. The mismanagement of healthy yearnings lights a path toward euthymia, if we learn how to notice the presence of these yearnings inside pathology and pivot in the direction of their healthy satisfaction.

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Specificity in the pursuit of euthymia

In their incisive paper, Fava and Guidi[1] argue that therapies, in addition to relief of symptoms or distress, should have the more ambitious goal of helping patients achieve a euthymic state that includes psychological well-being, positive affects, and flexibility. In a way, they are proposing that therapies go beyond the "gold standard" of remission to a "platinum standard" that could convey greater benefits in terms of quality of life and relapse prevention.

There is evidence from two investigations on well-being therapy (WBT) for depression that a focus on achieving well-being can lead to better relapse prevention than observed with clinical management or standard cognitive behavior therapy (CBT)[2]. But the only direct comparison of WBT and CBT for depression that measured well-being found significant improvements in one (personal growth) of the six domains in the Psychological Well-Being (PWB) scales for WBT and two domains (purpose in life and self-acceptance) for CBT[2]. Another small study comparing WBT with CBT for generalized anxiety disorder reported advantages for WBT in all six domains of the PWB scales.

In addition to WBT, Fava and Guidi note that two other evidence-based psychotherapies have features that may be useful in reaching states of euthymia. Mindfulness-based cognitive therapy (MBCT) includes methods intended to promote mindful, non-judgmental mentation that can help persons achieve a good life. Acceptance and commitment therapy (ACT) utilizes mindfulness and awareness to promote flexibility and acceptance.

WBT, MBCT and ACT each have appeal for pursuit of euthymia, because their proposed mechanisms of action and goals go beyond symptom relief. These therapies, especially WBT, have enriched our options for treatment by providing well-articulated methods for enhancing well-being. But it is not known whether treatments with specific methods for promoting well-being are required if the goals extend to achieving the "platinum standard" of euthymia.

A meta-analysis[3] of studies that employed either the PWB scales or the Mental Health Continuum – Short Form, assessing the six domains of well-being[1], found an overall moderate effect size for psychotherapies, of which the most common were WBT, mindfulness and ACT. However, the studies in this meta-analysis did not include several of the most widely used psychiatric treatments (e.g., pharmacotherapy, CBT and interpersonal psychotherapy), because investigations on these approaches have not utilized the above-mentioned scales.

Psychiatry and psychology have been driven largely by a "disease bias". Thus, outcome assessments in most treatment studies have focused heavily, or solely, on measuring symptom change – not on elements of psychological well-being. Yet, there is some evidence that approaches other than WBT, mindfulness and ACT may impact functions described by Fava and Guidi in their definition of euthymia.

For example, a meta-analysis of trials of antidepressants in patients with fibromyalgia[4] found a moderate effect size for pharmacotherapy on measures of well-being.

Other studies of antidepressants have reported positive changes in well-being after treatment with sertraline, levomilnacipran ER, venlafaxine and desvenlafaxine. These studies used a variety of scales to measure components of well-being, none of which were as comprehensive as the PWB scales. However, improvements in functions such as vitality, interpersonal functioning, and overall well-being suggest that antidepressants can yield benefits in addition to symptom relief.

There have been several studies suggesting that psychotherapies other than WBT, MBCT and ACT might be useful for reaching euthymia. In one such investigation, Iranian mourners treated with CBT had significantly greater improvements in spiritual well-being (defined as "stability in life, peace, balance and harmony, and feeling a close relationship with self, God, and the environment")[5]. Another study on CBT found greater benefit than an active control on emotional well-being[6], while research on CBT in HIV+ women documented significant increases in psychological and spiritual well-being compared to a psychoeducational control group[7]. Digital delivery of CBT also has been shown to improve well-being. Significant advantages versus control treatments were observed on Warwick-Edinburgh Mental Well-being Scale scores in an online CBT computer program for insomnia[8].

Logotherapy, a treatment focused primarily on helping patients find a sense of meaning in life, has been investigated rarely in randomized, controlled trials. But there is evidence that it can improve well-being. Purpose in life was enhanced in an investigation of individual logotherapy for paralyzed inpatients[9].

Occupational therapy, a treatment with a very different proposed mechanism of action, is another approach that may have benefit in reaching states of euthymia. A large investigation of this therapy versus a no-treatment control reported significant benefits in promoting well-being, including vitality, social functioning, and life satisfaction[10].

It is difficult to compare results of studies on well-being, because different designs and measures have been employed. Fava and Guidi's definitions of well-being and euthymia, and their measurement by the PWB scales, encompass more domains and functions than typically have been assessed in other studies. However, available evidence suggests that therapies that do not posit a specific mechanism of action for enhancing well-being may have some ability to help patients move toward euthymia.

Several explanations for lack of specificity in promoting well-being are possible. Symptoms of an illness such as depression interfere with experiences of well-being, so that any treatment that reduces symptoms may have potential for improving well-being. Furthermore, diverse treatment methods could enhance well-being by operating through common pathways such as effecting the neurobiological processes that underlie subjective experiences of psychological well-being. Unspecified or unmeasured therapeutic influences may be operative in improving well-being (e.g., positive placebo effect, behavioral activation, non-specific elements of all effective psychotherapies).

Although there has been insufficient research to support or refute these possible explanations, there are indications from earlier studies that specific hypothesized mechanisms of action may not be required to convey specific benefits. For example, antidepressants have been found to have a strong influence on negative thinking, a presumed purview of CBT, while CBT improves energy, interest and other symptoms that are targets for antidepressants.

Fava and his associates have been leaders in the development of WBT and in helping clinicians and researchers understand the importance of well-being as a treatment goal. Now, with their call for the pursuit of euthymia, they challenge us to significantly broaden our conceptualization of psychiatric treatment and to search for ways to assist patients in maximizing their functioning in domains such as personal growth, self-acceptance, and purpose in life.

WBT, MBCT and ACT offer considerable promise for reaching such treatment goals. But it is possible that other approaches also could promote well-being and the "platinum standard" of euthymia. Shouldn't all psychiatric treatments pursue euthymia as Fava and Guidi have defined it?

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Why the field of moral philosophy must guide any discussion on well-being

Fava and Guidi[1] argue that "clinical attention to psychological well-being requires an integrative framework which may be subsumed under the concept of euthymia". We welcome the call for psychiatrists to take an integrative approach to well-being that researches, debates, and fosters "positive" well-being in addition to just focusing on distress. The challenge will be achieving this whilst keeping the profession relatively free of value judgements on how people ought to live their lives.

Regrettably, a millennium of philosophical work has failed to find a way to

operationalize positive and negative well-being without either assuming that a person's own subjective assessment of his/her life is valid, or prescribing a definition about what constitutes a person's well-being. Whatever way forward psychiatry chooses, it must be done with full awareness of what assumptions are being made and how viable those assumptions may be.

One of the worst mistakes in psychiatry's history was the identification of homosexuality as a disorder prior to changes in the 1980s. This arose from adopting value definitions of what constituted a normal, "good" life, as supported by the psychoanalytic theories of the time. Since then, psychiatry has strived not to adopt value assumptions in favor of identifying disorder based on observations of clusters of objective symptoms. To ensure that symptoms do not simply represent healthy individual differences, diagnosis must also show that these symptoms cause clinically significant distress or significant impairment in an important domain of the individual's life.

The extent to which psychiatry has been successful in correctly identifying disorders in a value free manner remains a focus of debate, but the work of the last decades has been an attempt to do so. Should the field choose to embrace a wider positive well-being framework (or even individual indicators of positive well-being), then value judgements have to be radically reintroduced. Disorders are currently justified based on clusters of observed symptoms, which is likely to be supplanted by a neuropsychiatric framework when technology allows the specification of disordered biological functioning. Adding anything to this model involves value laden questions regarding what should be added, why, and on whose opinion should the inclusion be based. In doing so, we must remain aware that homosexuality was pathologized on the basis of expert opinion and seemingly valid assumptions, supported by a rigorously developed psychological model. It would be hubris to assume that in our age, unlike any prior, we are now able to decide what constitutes good functioning. This problem applies irrespective of whether one wants to replace the DSM, add additional considerations, or situate that manual within a larger framework.

Philosophically, apart from the absence of disorder, well-being can be defined either subjectively by the person's own opinion, or normatively by the satisfaction of externally defined criteria. Within economics and politics, there has been a focus on using people's own satisfaction with their lives as a subjective measure of their well-being, most simply by asking, on a 0 to 10 scale, "all things considered, how satisfied are you with your life?". This measure has recently been adopted by the Organisation for Economic Co-operation and Development (OECD)[2] – an intergovernmental organization with 36 member countries – as a core measure of societal performance, health care intervention, and policy.

This measure *appears* fair and value free, in that everyone can be measured on the same scale, and people are free to base their answer on whatever parts of their life they value and in whatever way they want to evaluate them. However, A. Sen was awarded Nobel Prize in economics partially for criticisms of this subjective approach. Briefly, he highlighted that people living in poverty with ill-health may consider themselves very contented, simply because they are not aware of any alternative[3]. Indeed, they could score higher than a wealthy person in a well-provisioned society. Similarly, people indoctrinated into believing that they are in a good situation (through state propaganda or cult control) may rate themselves as more satisfied with their life than other people. Subjective evaluations of one's own well-being require information and cognitive abilities; as such, adopting this approach may be particularly problematic when evaluating psychiatric patients.

If well-being cannot be wholly defined by the absence of disorder, nor the individual's own subjective judgement of his/her life, then this leaves only the normative approach based on criteria developed by others. The quality of these accounts have ranged from characteristics based on researchers' own views to the virtue ethics approach beginning with Aristotle[4], which has been subjected to millennia of evaluation and refinement based on the philosophical method. This method (of which science is a special case) involves logically exploring inconsistencies and paradoxes, and seeking to falsify theory by logical counterarguments. These well-articulated and defensible virtue ethics of what should comprise a set of criteria for well-being are extensively discussed in textbooks for undergraduate philosophy courses.

However, despite contemporary measures commonly thought of as linked to virtue ethics[5], the model is complex, and there are no measures of virtue ethics criteria currently available. This confusion is a good example of why engagement with philosophers is essential in order to understand and articulate the nuances of theory. Of course, not all normative approaches are based on virtue ethics, such as the WHO-5 Well-Being Index[6]. This entirely positively worded questionnaire of happiness has been designed to measure individuals on five specific domains of life. Regardless, all normative accounts of well-being specify for others what happiness is, and thus epitomize the exact form of value judgements that psychiatry has aimed to purge.

We value Fava and Guidi's provocative contribution to furthering a psychiatry that includes positive well-being, and we have made similar calls ourselves within clinical psychology to which any criticism would equally apply[7,8]. We are heartened to see the publication of these radical ideas in a mainstream psychiatry journal and encouraged by the appearance of their paper as the target article to be printed alongside commentaries. This is a very important debate to have.

However, our key point is that the debate must take full consideration of the (often deeply buried and unintuitive) underlying assumptions that are inherent in any definition of well-being, irrespective of whether the account is based on the absence of disorder, subjective, or normative accounts. Further, such a debate must be informed by the discipline of philosophy.

Since inception, philosophy has had this very debate on what constitutes well-being (or the "good life") and how it should be practically used. As such, regarding the nature of well-being, only philosophy has developed the relevant epistemological

tools, has produced most of the vast body of human knowledge on this subject, and still trains professionals specializing in this exact topic. Despite this, other fields have neglected this work and the opportunity for interdisciplinary collaboration. Such neglect has led to approaches already invalidated in philosophy and causing potential harm when applied. Psychiatry must not make this mistake.

As Fava and Guidi point out, the benefit to psychiatry of incorporating the right conceptions of positive well-being are huge. And so are the costs of getting it wrong.

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Euthymic suffering and wisdom psychology

In Fava and Guidi's paper[1], euthymia is defined by "lack of mood disturbances that can be subsumed under diagnostic rubrics", "positive affects" and "psychological well-being". So, good mood is euthymic. But, what about bad mood and suffering which can also *not* be subsumed under diagnostic rubrics? Life is no rose garden. All human beings experience illness, failure, conflicts with others, problems with children or spouse, financial troubles, or legal disputes. It would be a mental disturbance to feel happy under these circumstances. Is euthymia limited to positive affects or happy hours, or should it include all forms of "normal" mood?

That not all hardship and negative feelings automatically qualify as disorder is confirmed by the ICD-10, which provides separate codes (Z codes) for negative life situations such as loss of work, social exclusion, or burnout. If people feel unhappy when burdened by negative life events, this is no mental disorder, but "healthy suffering". It is of great importance not to medicalize such everyday problems[2]. In clinical practice, there are many people who contact medical experts because of healthy suffering. They need a professional evaluation together with some advice.

We need diagnostic criteria for healthy bad mood. Such criteria include situational adequacy of the type and intensity of the emotional reaction, self-appraisal, controllability, compliance with individual and social norms, lack of specific psychopathological signs and symptoms[3]. Healthy persons with normal bad mood display consistency in their behavior and values, show environmental mastery, self-acceptance, positive relations with others, flexibility, and resilience to go on with daily duties[4]. So, healthy suffering and bad mood should be included in the concept of euthymia.

How can interventions deal with such a broadened concept of euthymia? There are basically four different approaches to foster euthymia.

The first one is to get rid of bad mood by improving well-being through the increase of pleasant activities and experiences[5]. "Regeneration therapy"[6] engages people in positive and self-care exercises, from board games to cultural and social activities, relaxation and make oneself up. Positive effects of these interventions were shown in regard to depressed mood or distress intolerance and the ability to work. The bottom line is that, if you are under stress, you should do something positive for yourself or coddle yourself.

The second approach also aims to counteract bad mood, this time by teaching how to generate positive emotions directly. "Euthymia therapy"[7] teaches the art of enjoyment and experiencing of pleasures. "Well-being therapy"[1] teaches people to focus on constituents of positive mood by self-observation, change of dysfunctional cognitions, and promotion of activities. Studies on these interventions showed positive effects in depressed or psychosomatic patients transdiagnostically. The bottom line is to improve the capacity of the individual to generate positive emotions.

A different type of approach is represented by "mindfulness and acceptance" based therapies[8]. Their primary goal is not to get rid of negative emotions and cognitions, but instead to change the individuals' relationship to their emotional state, their experiences, and the living context. This is done by encouraging awareness and acceptance of unpleasant feelings through mindfulness practice and cognitive defusion. Commitment and behavior change processes are based on contact with the present moment. Bad mood is accepted and may still be present after treatment. This approach implicitly has a broader concept of euthymia, including bad and positive mood alike. The bottom line is to accept and arrange oneself with something that cannot be changed.

Another approach, which goes in the same direction, is "wisdom therapy"[9]. Life span psychology describes wisdom as a psychological capacity, given to all persons, which is essential in coping with severe, irreversible or unsolvable problems, but also in dealing with daily dilemmas, such as the decision whether to stay at home with a sick child or to go to work. Similar to other psychological capacities, there are about a dozen sub-dimensions, such as recognition of reality (factual and procedural knowledge, contextualism, relativization of problems and aspirations), mastery of emotions (perception and acceptance of emotions, serenity), acceptance of personal limitations (self-relativization, self-distance), clarification and self-assurance of goals and values (value relativism, forgiveness and acceptance of the past, uncertainty tolerance, long-term perspective),

and interactional competencies (change of perspective, empathy).

"Wisdom therapy" provides strategies to translate these sub-dimensions into treatment. There is evidence that it works in patients with severe adjustment disorders[9]. The goal of the intervention is to learn how to deal with bad and good times alike. Euthymia can be defined as a state of wisdom, in which persons feel at ease with themselves and the world, their past, the present and the future, in good and bad times, and do not lose heart and courage in the face of adversities and hardship.

The concept of euthymia should reflect the daily existence of human beings. Happiness is limited to very few moments in life. Demands, hardship, burdens fill the rest of time. Back pain, heavy work or driving a car in combusted streets do not produce happiness. But there is nevertheless euthymia. The problem of mental illness is that people are overburdened and impaired by daily hassles, while healthy persons have resilience and can deal with bad times.

We should not create the misunderstanding that happiness is the goal to be pursued by our interventions. This can lead to disappointment. Instead, mastery of exceptional and daily burdens and demands, and how nevertheless to "feel OK" (not happy but euthymic), should be the aim.

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Understanding mood in mental disorders

Mood symptoms and disorders have become a major health issue and the leading cause of disability worldwide. In most branches of medicine, physiology builds the basis of pathophysiology. Psychiatry, instead, lacks a scientifically sound idea of normal functioning. This is particularly true for mood. Psychiatric classification systems conceptualize low mood and mood fluctuations as mere pathologies. Positive psychology constantly confounds optimistic mood with mental health. The paper by Fava and Guidi[1] is a refreshing alternative to these mainstream approaches to mood and its disorders. Importantly, the authors' integrative framework takes mood's adaptive function into account.

The biological mechanisms underlying mood are highly conserved and widespread across species[2]. This suggests that mood has an essential function for survival and reproduction. The brain reward system is an important center of mood regulation. Throughout evolution, this system has increased in relative size from rodents to humans, suggesting that mood is more important in humans than in other animals[3]. What are mood's ancestral and present functions?

From an ecological perspective, mood functions as a slowly changing decision-making mechanism that regulates the individual approach and avoidance behavior. This regulation is based on the expected reward rate over a longer period of time[2]. Clinicians are used to focus on easily remembered life events in the past – rather than changes in expected reward rates in the future – when exploring the causes of distress and negative emotions. This frequently leads to a misunderstanding of mood states that are detached from any immediate triggering stimulus. A good example is given by seasonal mood fluctuations that are caused by a slow unnoticed reduction or increase of the light reward rate[4]. The American poet E. Dickinson depicted this nature of mood regulation in her poem "As imperceptibly as grief, the summer lapsed away", linking mood cycles to cycles in the environment.

In scientific terms, mood integrates perceptions and emotional experiences over time. When a person experiences a series of non-rewards or punishments over time, he/she may develop depressed mood. It usually needs an enduring safe situation and repeated rewards to change this negative, risk-aversive attitude and to improve expectations about the future reward rate. What is the function of this emotional spill-over? It reflects a specific assumption about the environment, namely that threats and rewards come in cycles. In the Stone Age, a dried up blackberry bush predicted more dried up bushes. A successfully hunted gazelle predicted more hunting luck. In many instances, rewards and non-rewards still come in cycles and mood is adaptive. However, when applying for jobs or looking for a partner in a big city, the rates of rewards and punishments may not by cyclic but random. As a result, emotional spill-overs can be dysfunctional. Clinicians should help patients to differentiate functional from dysfunctional mood by estimating future reward rates in individual situations.

In humans, mood has a subjective valence. However, mood also regulates more primary cognitive and physiological systems of an organism, such as activity levels and the threshold for detecting rewards and threats, also referred to as cognitive bias. It is important that clinicians distinguish these aspects of mood, because their neural substrates differ. Serotonergic neurotransmission is particularly important for mood as subjective valence and cognitive negativity bias, while catecholamines regulate motivation and activity levels[5].

Evolutionary psychiatrists explain the high prevalence of low mood by referring to the "smoke detector principle"[6]. This posits that, in the face of uncertainty, mood regulation prefers low mood over high mood because the result of high mood may be death through overlooking risks, while the costs of low mood include missed opportunities and suffering, which do not weigh heavily in the light of evolution. As a result, it is important to detect uncertainty in the

subjective calculations of future reward rates in patients suffering from low mood.

The increasing prevalence of suffering from maladaptive mood regulation may reflect a mismatch between mood and modern environments. There has been a dramatic decrease in environmental risks, reflected by dropping rates of wars, homicides and numbers of dangerous animals. As a result, mood systems look more and more like sensitive and error-prone smoke detectors in a world where candles, fire heating and smoking have become out of fashion. Moreover, mood is not specific for a certain domain[7]. One cannot have at the same time a high mood at work and a low mood in the family. Mood is general, possibly because in ancient times reward opportunities were highly correlated. A flood destroyed almost all of them.

Another good example of a possible mood-environment mismatch is grief. In our ancestral environment, grief may have had the function to motivate searching for loved ones who simply did not return to the camp[8]. Nowadays, grief is mostly a response to a definitive loss in which prolonged sadness has become maladaptive. Vivid memories, hallucinated voices and felt presence of a meaningful other prepares for a costly and futile search. As a result, modern psychiatry has good reasons to develop therapeutic strategies for individuals suffering from prolonged grief.

Because the relationship between mood and environment is subjective, mostly unconscious and complex, psychiatry has the tendency to completely ignore this relationship. In the DSM-5, the environment does not play a role when diagnosing mood disorders. Low mood associated with symptoms such as anhedonia, low energy levels and negative thinking defines a major depressive episode. This diagnostic concept makes sense in an environment with a constantly high reward rate. However, not all environments on this planet comply with this description. Our diagnostic systems hold the danger of medicalizing real social and environmental problems. Dysthymia and mild depression may be an adaptive response to prolonged and realistically expected enduring adverse conditions. As a result, it is important for clinicians to carefully consider the individual life circumstances in which a mood disorder develops. Facing enduring adversity, therapy-induced optimism and mood enhancing drugs may increase the risk of physical and mental traumatization and even death[2].

Taken together, an evolutionary view helps to see mood as the product of interactions between neurobiological mechanisms and the structures we give to our societies and environments. Fava and Guidi's approach has the potential to identify these interactions and to foster the development of individual therapeutic plans that correspond to them.

In Fava's well-being therapy, self-observation and structured diary help to identify complex influences of the environment on well-being over longer periods of time[9]. The focus on positive situations and euthymia allows for the identification of expected reward rates that are crucial for mood regulation. Balanced functioning, flexibility, adaptation, openness, stage-dependent learning, awareness, macroanalysis, acceptance, autonomy, growth and flourishing are the key words of this timely and promising approach.

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The untapped power of allostasis promoted by healthy lifestyles

Fava and Guidi[1] write: "Psychiatrists often consider the positive characteristics displayed by a patient in their clinical judgment; yet current assessment and treatment strategies are shifted on the side of psychological dysfunction". Similarly, the word "stress" is commonly used to emphasize the negative aspect of the experiences to which we adapt daily; and this is done in such a way as to implicate cortisol as responsible for negative consequences, without also recognizing the positive role of cortisol and other physiological mediators in promoting adaptation and maintaining health in response to all experiences, whether or not we call them "stressful".

Indeed, the word "stress" is used in several ways so as to make it ambiguous. "Good stress" involves our taking a chance on something we want, such as interviewing for a job or school, or giving a talk before strangers and feeling rewarded when we are successful. "Tolerable stress" means that something bad happens, like losing a job or death of a loved one, but we have the personal resources and support systems to weather the storm. "Toxic stress" means that, when something bad happens, we do not have the personal resources or support systems, and, as a consequence, we lack a sense that we have some control. We may then suffer mental and physical health problems over time, particularly if the situation is not resolved.

Now, let us put these three forms of "stress" into a biological and behavioral context. We know that "homeostasis" means the physiological state which the body maintains to keep us alive – that is, body temperature and pH within a narrow range, and adequate oxygen level. In order to maintain homeostasis, our body activates hormone secretion as well as the autonomic and central nervous system to help us adapt, for example, when we get out of bed in the morning, walk up a flight of stairs, or have a conversation. These systems are also turned on when we are surprised by something unexpected, or get into an argument, or run to catch a train.

Using the word "stress" does not really recognize all of the underlying biology, while the word "allostasis" focuses on the active process of adaptation to many challenges, whether not we call them stressful[2]. "Allostatic load" is a term that refers to the cumulative changes in the body and brain that are produced by dysregulation and overuse of the "mediators" of allostasis[2,3].

The basic concept behind allostatic load is an outgrowth of Sapolsky's "glucocorticoid cascade hypothesis" of stress and aging[4], that was broadened to encompass not only glucocorticoids but also other interacting mediators of adaptation, and to include protective/adaptive as well as damaging effects of those mediators.

The "mediators" help us adapt as long as they are turned on in a balanced way when we need them, and then turned off again when the challenge is over. When that does not happen, they can cause unhealthy changes in brain and body. This is also the case when they are not produced in an orchestrated and balanced manner – for example, too much or too little cortisol or an elevated or too low blood pressure – leading over weeks and months to "allostatic load". When the wear and tear is strongest, we call it allostatic overload, and this is what is occurring in toxic stress[5]. An example is when hypertension leads to a heart attack or stroke and abdominal fat contributes chemicals that accelerate the coronary artery blockade and increase stroke risk.

One essential aspect of allostasis and allostatic load/overload is how the brain responds. We now know that genes are turned on and off epigenetically by experiences over the life course[6], and that there is an adaptive structural plasticity of synapses, some of which are eliminated while others are formed during the daily circadian day-night cycle, as well as following acute and chronic stressors[7].

The dendrites of neurons in brain areas such as the hippocampus, prefrontal cortex, amygdala and nucleus accumbens can shrink or grow and become less or more branched as a result of experiences, including those referred to as "stressful". A healthy brain shows resilience and recovery after the stressful experience is over. Yet, after a stroke, head trauma or seizure, there can be permanent irreversible damage and neuron loss due to allostatic overload, involving excitatory amino acids, cortisol and other mediators. Nevertheless, after a stroke, compensatory brain plasticity can help reduce the damage[8].

How does this relate to euthymia and positive aspects of health? Fava and Guidi state: "The findings indicate that flourishing and resilience can be promoted by specific interventions leading to a positive evaluation of one's self, a sense of continuing growth and development". Moreover, they emphasize that the pursuit of euthymia is not a therapeutic intervention for specific mental disorders, but a transdiagnostic strategy to be incorporated in an individualized therapeutic plan. Here, plasticity and resilience of the brain is essential.

Translated into the language of stress biology, euthymia means using allostasis optimally and maintaining a healthy balance that promotes positive aspects of brain and body health through health-promoting behaviors. These behaviors involve not only diet, but also adequate and good quality sleep, positive social interactions, as well as a positive physical environment that is safe and includes green space, all of which reduce allostatic load. Regular physical activity benefits the brain as well as the body and does so, at least in part, by increasing generation of new neurons in the hippocampus and, as a result, counteracting depression and improving aspects of memory. These basic health-promoting behaviors that promote allostasis can help the self-healing process, since the inherent adaptive plasticity of the brain can operate more effectively.

But the most provocative and far-reaching implication, even beyond euthymia, is the reported physiological difference between an eudaimonic lifestyle involving meaning and purpose and an hedonic lifestyle involving seeking and finding pleasure. According to Fredrickson et al[9], people with an hedonic lifestyle show in their white blood cells a higher expression of pro-inflammatory genes and a decreased expression of genes involved in antibody synthesis and type I interferon response, compared to those with a eudaimonic lifestyle, who show the reverse[9] and thus a lower allostatic load.

Fredrickson et al go on to suggest that hedonic and eudaimonic lifestyles engage different gene regulatory programs, despite their similar effects on total well-being and depressive symptoms. They argue that "the human genome may be more sensitive to qualitative variations in well-being than are our conscious affective experiences". Clearly, this provocative idea requires an even deeper exploration of those aspects of psychological well-being, positive thinking and euthymia than is currently available.

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Euthymia and disabling health conditions

The focus of positive psychology can be seen as an attempt to address the philosophical question first put forth by the ancient Greeks: "what does it mean to live a good life?". When people's physical body changes and the person-environment interaction significantly alters due to a chronic illness/disability condition, this question can take on additional di-

mensions and importance.

For example, after a stroke or a spinal cord injury, people often wonder what the future has now in store for them. Questions such as "what am I supposed to do now?" are frequent and applied to both their personal and work lives. Rates of depression within this population range between 10 and 60%[1], and individuals with a spinal cord injury have rates of post-traumatic stress disorder (PTSD) as high as 14% six months post-injury[2].

People with spinal cord injury who develop depression are likely to experience longer hospitalizations, increased pain, higher financial expenditures, as well as decreased self-efficacy and diminished quality of life[3]. They need to maintain an extensive and complex self-care regimen in order to prevent complications such as pressure ulcers, skin injuries and urinary tract infections. Active self-care can significantly mitigate these negative outcomes; however, sustaining a self-care regimen when living with depression is quite challenging.

Once entering rehabilitation to address a disabling health condition, the most important goal is to help individuals attain the highest possible levels of well-being. Mindfulness interventions can significantly reduce depression, anxiety and pain in individuals with spinal cord injury[4]. Utilizing a variety of positive psychology interventions in individuals with chronic pain has been found to result in significant improvements in pain intensity, pain interference, life satisfaction, positive affect, and depression, when compared to a control group. Importantly, these improvements persisted in a 2.5-month follow-up[5].

Researchers who have examined more general factors of quality of life and adjustment to chronic illness/disability have found that those who adjust well perceive their current life as in continuity with their personal biography, and focus on their continued capability and competence rather than solely on areas of inadequacy and limitation. These individuals acknowledge that they are the same person as they were pre-injury, but just have more challenges[6].

Leisure activities such as good acts (e.g., volunteering) or good habits (e.g., regular exercise) have likewise been found to contribute to post-traumatic growth, by providing opportunities to discover unique abilities and hidden potential, build companionship and meaningful relationships, make sense of the traumatic experience, find meaning in everyday life, and generate positive emotions[7]. It is of interest to note that these elements mirror the dimensions of well-being described by Fava and Guidi[8].

Applying the concept of euthymia to persons living with a disability argues for a more comprehensive appreciation of the strengths remaining in each person's "new normal" circumstances while maintaining a focus on the perceived difficulties.

With euthymia emphasized, it would be expected that individuals would be more likely to expend increased effort in the rehabilitation process, possibly resulting in increased engagement in self-care. This, in turn, could lead to decreased future hospitalizations and improved overall quality of life. In this manner, individuals with increased euthymia could be expected to make further functional improvements after rehabilitation.

Given the current emphasis on both preventing disease and increasing levels of health, it is even more important to learn how to facilitate these outcomes. Unfortunately, this hoped-for state of affairs currently remains an unanswered set of empirical questions that beg to be addressed with data. Luckily, these studies could be facilitated by currently available valid and reliable psychometric instruments to assess the various elements of euthymia[8].

It is understood that adjusting to a life with a disability is challenging. As R. Trieschmann stated in writing about the more personal dimensions of living with a spinal cord injury, "people with this injury are a fairly heterogeneous group, but they have one thing in common: the disability penalizes them and reduces their freedoms"[9]. By increasing euthymic adaptations, this very real "penalization" and "reduction of freedom" could be understood and reacted to in a different light. The use of this type of intervention could, and should, be expanded to other conditions such as limb loss, brain injuries, and a variety of chronic illnesses.

Utilizing a euthymic framework could lead to a significant improvement in quality of life and well-being in a rehabilitation population. In such a model, building up new psychological strengths can facilitate the adaptation to the substantial life changes accompanying chronic illness/disability.

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The pursuit of euthymia: are cultural factors relevant?

Fava and Guidi[1] quote the definition of euthymia by Democritus, as a state of quiet satisfaction and balance of emotions. In the Indian context, there are two related cultural concepts which can be considered similar to euthymia, i.e. equanimity and equipoise.

In the Buddhist literature, the term "equanimity" indicates a mental state or trait that cannot be swayed by biases and preferences[2], an "even-mindedness in the face of every sort of experience, regardless

of any pleasure or pain"[3], and "a balanced reaction to joy and misery, which protects one from emotional agitation"[4,5].

Equanimity has not been much discussed in the context of Western psychological theories[4], but it emerges in related concepts such as acceptance, non-judgment, non-striving, and non-reactivity – especially in the context of mindfulness meditation practice.

Desbordes et al[4] reviewed the psychological, physiological and neuroimaging aspects of equanimity, and proposed that it potentially captures the most important psychological elements of well-being. To rephrase its definition in modern terms, equanimity is an even-minded mental state or dispositional tendency toward all experiences or objects, regardless of their affective valence (pleasant, unpleasant or neutral) or source[4].

Equanimity of mind is being able to keep the mind steady, balanced in all the conditions of life, contented, calm and peaceful. Equanimity is having the ability to remain cheerful in adverse conditions, to face danger, and to have the presence of mind and forbearance to bear insult, injury and persecution, without getting emotionally affected[6]. This description is close to the original derivation of the term euthymia (Greek origin: *eu*, well, and *thymos*, soul).

Measuring equanimity, both subjectively and objectively, presents several challenges. Equanimity may be difficult to distinguish from apathy, indifference and emotional coldness, as well as from other situations with diminished emotional responses to a given stimulus.

The concept of "equipoise" refers to a state which allows expression of empathy without letting subjective or reactive responses cloud one's judgment. "Emotional equipoise" describes a balanced and rational mental state, irrespective of external stimuli[7].

Equanimity and equipoise may appear to be indicating "optimal balanced well-being", which is likely to vary from person to person based on socio-cultural and spiritual factors. They are dynamic states lying on a continuum, interrelated and difficult to assess using normative metrics.

Gross et al[8] have developed an affect regulation perspective of well-being. Desbordes et al[4] have described equanimity as an emotion regulation strategy that can change both the magnitude and quality of responses. If euthymia is an affective state, it is probably arising from adaptive affect regulation and generation, like equanimity. However, emotions have more dimensions than just affect, i.e., the behavioral, cognitive and somatic components. Feelings are also expressed in bodily forms, in metaphors and idioms, and as idioms of distress. On the other hand, some patients consider euthymia distressing, complain of being "unable to feel" and make attempts to expose themselves to situations which can arouse feelings, or have a feeling of feeling – a meta-emotion.

In terms of management, both psychotherapy and pharmacotherapy (mood stabilizers) probably help the person to achieve euthymia. However, many of us have the experience of patients on lithium prophylaxis complaining of having lost the creativity, spark, zing or zeal they had before the illness started and the drug was prescribed to them. They may be rated as euthymic on rating scales, but feel different from their premorbid self. In these cases, euthymia may not be the ideal recovery goal. Complementary and alternative modes of treatments, such as yoga and mindfulness, may be needed to achieve equanimity.

The pursuit of euthymia will hopefully raise a debate on a more universally acceptable model of emotions, their variations and disturbances. One can agree partly with Fava and Guidi that psychological well-being needs an integrative framework which may be subsumed under the concept of euthymia. The constructs of equanimity and equipoise could be considered in this context, however challenging this may turn out to be.

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20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20)

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Antipsychotics are effective in preventing relapses of schizophrenia, but it is generally believed that their long-term use is harmful for patients' physical well-being. However, there are no long-term studies which have verified this view. This nationwide, register-based cohort study aimed to assess the risk of hospitalization due to physical health problems, as a marker for severe physical morbidity, and the risk of all-cause mortality, as well as of cardiovascular and suicidal death, associated with antipsychotic use in all patients treated for schizophrenia in inpatient care between 1972 and 2014 in Finland (N=62,250), with up to 20 years of follow-up (median: 14.1 years). The use of antipsychotic drugs (i.e., use of any antipsychotic compared with non-use) and the use of specific antipsychotics were investigated, and outcomes were somatic and cardiovascular hospitalization, and all-cause, cardiovascular and suicide death. Hospitalization-based outcomes were analyzed by a within-individual design to eliminate selection bias, comparing use and non-use periods in the same individual by stratified Cox model. Mortality outcomes were assessed by traditional between-individual Cox multivariate models. The adjusted hazard ratios (aHRs) for any somatic hospitalization and cardiovascular hospitalization were 1.00 (95% CI: 0.98-1.03) and 1.00 (95% CI: 0.92-1.07) during use of any antipsychotic compared to non-exposure periods within the same individual. The aHRs were 0.48 (95% CI: 0.46-0.51) for all-cause mortality, 0.62 (95% CI: 0.57-0.67) for cardiovascular mortality, and 0.52 (95% CI: 0.43-0.62) for suicide mortality during use vs. non-use of any antipsychotic. The most beneficial mortality outcome was associated with use of clozapine in terms of all-cause (aHR=0.39, 95% CI: 0.36-0.43), cardiovascular (aHR=0.55, 95% CI: 0.47-0.64) and suicide mortality (aHR=0.21, 95% CI: 0.15-0.29). The cumulative mortality rates during maximum follow-up of 20 years were 46.2% for no antipsychotic use, 25.7% for any antipsychotic use, and 15.6% for clozapine use. These data suggest that long-term antipsychotic use does not increase severe physical morbidity leading to hospitalization, and is associated with substantially decreased mortality, especially among patients treated with clozapine.

Key words: Schizophrenia, antipsychotic treatment, physical morbidity, hospitalization, all-cause mortality, cardiovascular mortality, suicide, clozapine

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Antipsychotics are effective in preventing relapses in schizophrenia, according to both randomized controlled trials (RCTs)[1] and observational studies representing real-world patients with long follow-up periods[2]. However, antipsychotic use is associated with the risk of serious adverse events, such as tardive dyskinesia[3,4]. In addition, adverse effects of antipsychotic drugs on physical health are numerous[5-7]. In short-term treatment, the use of these medications has been associated with weight gain, dyslipidemias, glucose metabolism dysregulation, QTc prolongation and sudden cardiac death[8-11], and many of these adverse effects have been linked with their pharmacological action[9,11,12]. Nevertheless, there is a lack of knowledge about whether these cardiometabolic adverse effects are associated with greater physical morbidity and mortality in long-term use[13,14].

According to a meta-analysis based on studies from various countries, persons with schizophrenia have a 14.5 years shorter average life expectancy compared with the general population[15]. Our recent findings from a large, nationwide cohort study showed that the gap in longevity has remained the same during the last 30 years[16]. This unchanged excess mortality compared with the general population was explained by a simultaneous decrease in suicides and increase in cancer and cardiovascular deaths among persons with schizophrenia.

Persistent premature mortality in schizophrenia might also be attributed to long-term antipsychotic use. However, recent systematic reviews and meta-analyses of short-term placebo-controlled RCTs have found an about 30-50% lower mortality risk in association to antipsychotic use compared with non-use[17,18], although the duration of treatment was not identical for active vs. placebo arms in one of these studies[18], and the statistical power was insufficient to reach a significant difference in the other[17].

Large observational studies have also reported beneficial effects of antipsychotics on all-cause mortality, which has been attributed to more healthy lifestyle behaviors, less psychosis-related cortisol increase, and increased secondary prevention due to engagement with the medical system in antipsychotic-treated patients[19-22].

Data on long-term physical morbidity and mortality associated with antipsychotic use are lacking[1], which would be crucial knowledge for a more in-depth assessment of the long-term risk-benefit ratio of the use of these medications in the treatment of schizophrenia[13]. Thus, we aimed to study the risk of hospitalization due to physical health problems, as a marker for severe physical morbidity, and the risk of all-cause mortality as well as cardiovascular and suicidal death associated with antipsychotic

use in a nationwide cohort of persons with schizophrenia, with up to 20 years of follow-up.

METHODS

Study population

The study population was identified based on the nationwide Hospital Discharge register, which is managed by the National Institute of Health and Welfare. The study cohort included all persons treated in inpatient hospital care due to schizophrenia in Finland during the period 1972-2014[2,23]. Schizophrenia was defined by discharge diagnosis (ICD-10 codes F20 and F25; ICD-9 and ICD-8 codes 295*).

The whole cohort (named as prevalent cohort) included 62,250 persons with schizophrenia, while the incident cohort (first-episode patients) included 8,719 persons who were hospitalized for the first time due to schizophrenia in the period 1996-2014, and who had not used antipsychotic drugs during the year preceding the index hospitalization.

The follow-up started on January 1, 1996 for the prevalent cases, and at the first discharge from inpatient care for the incident cases. The follow-up time ended at death or on December 31, 2015, whichever occurred first.

Exposure

As drug dispensing in the Prescription register data is recorded according to Anatomical Therapeutic Chemical (ATC) classification codes, we derived antipsychotics as class N05A, with exclusion of lithium. The PRE2DUP method was utilized to derive drug use periods, i.e., when drug use started and ended, based on purchase dates, amounts of drugs dispensed and personal drug use patterns[24].

Outcomes

Two inpatient care-based outcomes were defined: somatic hospitalization (all hospitalizations except psychiatric ones, i.e., excluding ICD-10 codes F* as main diagnoses) and cardiovascular hospitalizations (ICD-10 codes I00-I99). Three mortality outcomes were analyzed: all-cause mortality, cardiovascular mortality (ICD-10 codes I00-I99) and suicide death (X60-X84). Follow-up for mortality in hospital care was censored after the first seven days, due to lack of drug data during hospital care. Sensitivity analyses for all-cause mortality were conducted without this censoring.

Statistical analyses

Hospitalization-based outcomes (somatic and cardiovascular hospitalization) were analyzed by a within-individual design, which is suitable for recurrent events. A stratified Cox proportional hazard regression model[25] was utilized, in which each individual formed his/her own stratum, and the risk of outcome was compared between exposure and non-exposure periods for each person. The follow-up time for each individual was reset to zero after each outcome event. In within-individual analyses, all time invariant covariates (such as genetics and gender) are controlled for in the design, and only time-varying covariates are adjusted for. These covariates were the temporal order of exposures, time since cohort entry, and use of other psychotropics (antidepressants, benzodiazepines and related drugs, lithium and other mood stabilizers).

Mortality outcomes were analyzed by traditional multivariate-adjusted Cox regression models. These analyses were adjusted for gender, age at cohort entry, year of cohort entry, time since diagnosis, number of prior psychiatric hospitalizations, temporal order of exposure to antipsychotics, other medication use, non-adherence, prior use of long-acting injectable (LAI) antipsychotics, prior suicide attempt, substance abuse and physical comorbidities.

Sensitivity analyses were conducted among incident patients, and by excluding the first ten years of follow-up from the analyses for each person (long-term survivors). Long-term survivors were analyzed to explore longer-term effects on all-cause mortality after patients had passed the highest risk time for suicide[26]. In addition, time-dependent Kaplan-Meier curves for all-cause mortality were drafted to describe the mortality hazard of antipsychotic use versus non-use, and for the ten most commonly used antipsychotics.

Monotherapy periods of specific antipsychotics were analyzed, with all periods including more than one antipsychotic coded as "polytherapy". Additional analyses were conducted with "any therapy" models, where use of a specific drug was assessed as "yes" or "no", independent of concomitant use of other antipsychotics (but adjusted for this variable). The threshold of significance for p values was corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate method.

To assess cumulative exposure, sensitivity analyses on cumulative proportion of days exposed to antipsychotics during outpatient observation time were conducted in a nested case-control design for incident patients. Days of exposure to antipsychotic drugs were divided by outpatient observation time, resulting in categorization as 0% (full non-adherence), >0 to <80% (partial non-adherence) and ≥80% (adherence). Outcomes were all-cause and cardiovascular mortality.

The research project was approved by the Ethics Committee of the Finnish National Institute for Health and Welfare. Further permissions were granted by pertinent institutional authorities at the Institute, the Social Insurance Institution of Finland, and Statistics Finland.

RESULTS

At the start of follow-up, the median age was 45.6 years (interquartile range, IQR=34.6-57.9; mean=46.8) in the prevalent cohort (N=62,250), and 36.2 years (IQR=26.2-52.3, mean=41.2)

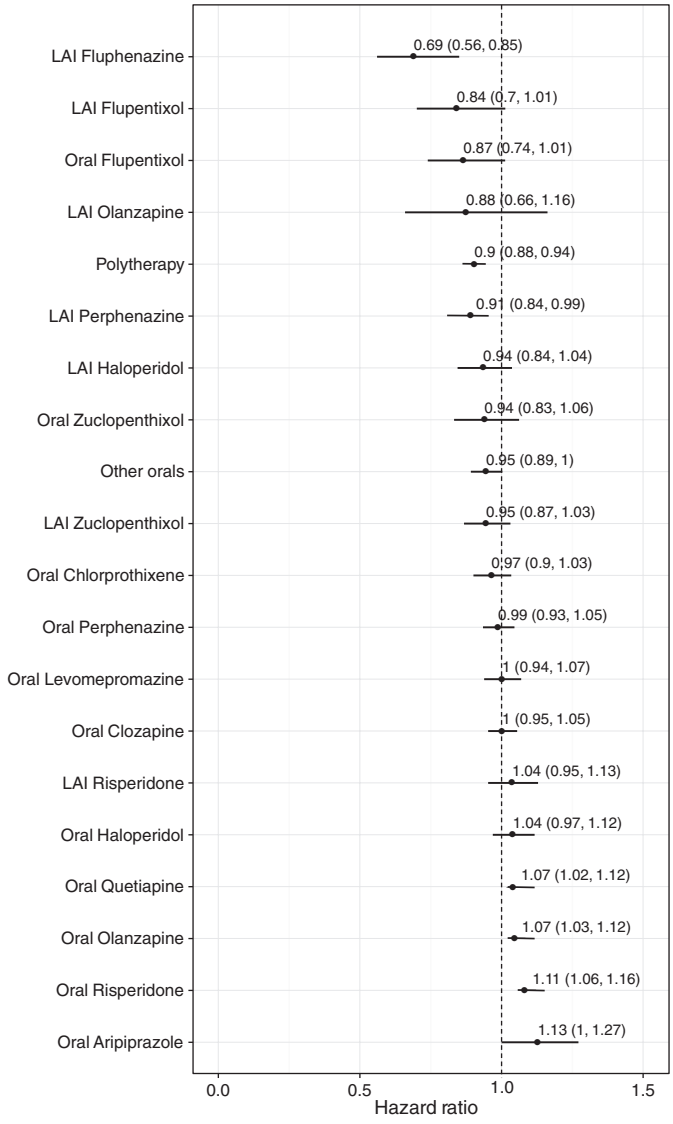

Figure 1 Risk of somatic hospitalization during monotherapy with specific antipsychotics compared with no use of antipsychotics in the prevalent cohort (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

in the incident cohort (N=8,719). The proportion of males was 50.2% in the prevalent cohort and 56.2% in the incident cohort. The prevalence of comorbid conditions at baseline in the prevalent cohort was as follows: 4.0% for alcohol or substance abuse, 4.8% for cardiovascular disease, 5.1% for diabetes, 0.2% for liver disease, and 0.8% for renal disease.

The median follow-up time was 14.1 years (IQR=6.9-20.0) for the prevalent cohort and 10.1 years (IQR=5.0-14.3) for the incident cohort. During the follow-up, 13,889 (22.3%) persons of the prevalent cohort died, and 42,271 persons (67.9%) experienced somatic hospitalization. The corresponding figures for the incident cohort were 1,160 (13.3%) and 4,488 (51.5%). When censoring to >7 days hospitalizations, the median follow-up time was 13.2 years (IQR 6.2-19.3) in the prevalent cohort, and 9.4 years (IQR 4.5-13.6) in the incident cohort.

Antipsychotic use in monotherapy was not associated with an increased risk of somatic hospitalizations (adjusted hazard ratio, aHR=1.00, 95% CI: 0.98-1.03) compared with non-exposure periods within the same individual (153,149 somatic hospitalizations per 579,306 person-years of antipsychotic use vs. 49,717 somatic hospitalizations per 188,107 person-years of non-use).

Among specific antipsychotics, LAI fluphenazine was associated with the highest decrease of risk (HR=0.69, 95% CI: 0.56-0.85), whereas quetiapine, olanzapine, risperidone and aripiprazole were associated with a slightly increased risk of somatic hospitalizations. Point estimates for the majority of other antipsychotics were around 1.0, with CIs crossing 1.0 (Figure 1).

Mainly similar results were observed for specific antipsychotics used in any therapy (with or without concomitant other antipsychotics), and when within-individual monotherapy model was additionally adjusted for use of somatic co-medications.

Antipsychotic use was not associated with an increased risk of cardiovascular hospitalization (aHR=1.00, 95% CI: 0.92-1.07) compared with non-use periods within the same individual. LAI fluphenazine in monotherapy was associated with a significantly

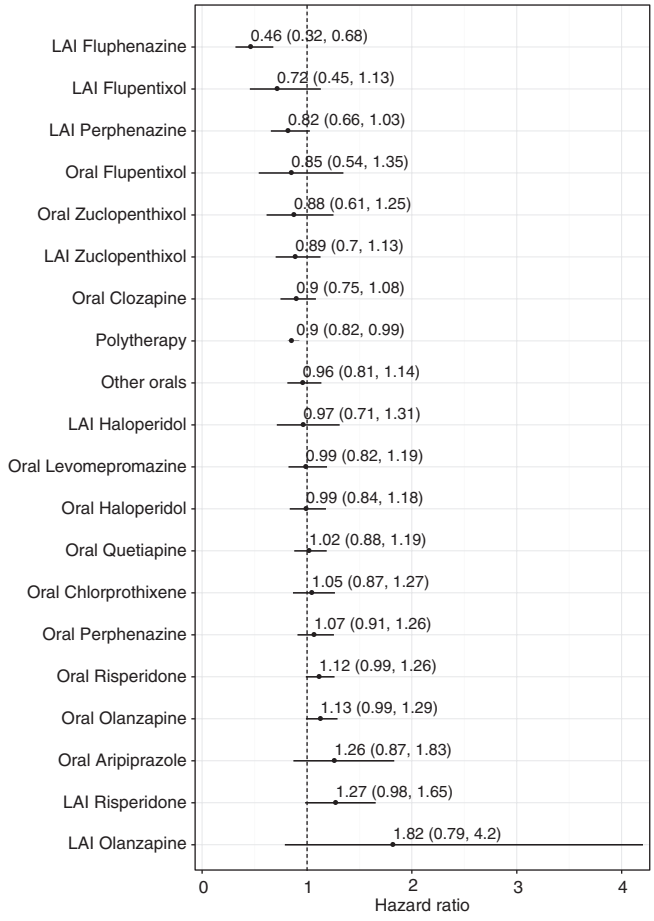

Figure 2 Risk of cardiovascular hospitalization during monotherapy with specific antipsychotics compared with no use of antipsychotics in the prevalent cohort (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

decreased risk of cardiovascular hospitalization (aHR=0.46, 95% CI: 0.32-0.68) (Figure 2).

All-cause mortality was significantly lower in patients using any antipsychotic compared with those using none (Figure 3). In Kaplan-Meier analyses, the cumulative mortality rates during follow-up up to 20 years were 46.2% for non-use, 25.7% for any antipsychotic use, and 15.6% for clozapine use (p<0.0001). The aHR for all-cause mortality was 0.48 (95% CI: 0.46-0.51) during antipsychotic use compared with non-use in the prevalent cohort (8,264 deaths per 577,417 person-years of antipsychotic use vs. 5,635 deaths per 187,773 person-years of non-use). The corresponding figure in the incident cohort was aHR=0.64 (95% CI: 0.55-0.75) (540 deaths per 55,069 person-years of antipsychotic use vs. 620 deaths per 25,634 person-years of non-use).

Most of the specific antipsychotics in monotherapy were associated with a lower risk of death (Figure 4), with similar results in any therapy analyses.

Cardiovascular mortality was also significantly lower (aHR= 0.62, 95% CI: 0.57-0.67) during any antipsychotic use compared with non-use in the prevalent cohort. The corresponding figure in the incident cohort was aHR=0.83 (95% CI: 0.63-1.09). No specific antipsychotic was associated with an increased risk. Instead, several antipsychotics were associated with a significantly reduced cardiovascular death risk compared with no use (aHR=0.14, 95% CI: 0.02-1.01 for LAI olanzapine; aHR=0.24, 95% CI: 0.11-0.54 for oral flupentixol) (Figure 5).

Suicide mortality was significantly lower (aHR=0.52, 95% CI: 0.43-0.62) during antipsychotic use compared with non-use in the prevalent cohort. The corresponding figure in the incident cohort was aHR=0.50 (95% CI: 0.33-0.74). Several antipsychotics were associated with a reduced suicide mortality (Figure 6).

Overall, the most beneficial mortality outcome was associated with clozapine, considering all-cause (aHR=0.39, 95% CI: 0.36-0.43), cardiovascular (aHR=0.55, 95% CI: 0.47-0.64) and suicide mortality (aHR=0.21, 95% CI: 0.15-0.29). Clozapine was used by 14,350 (23.1%) of persons at some point during the follow-up. The weakest mortality outcome was associated with levomepromazine, considering all-cause (aHR=0.82, 95% CI: 0.71-0.93), cardiovascular (aHR=1.02, 95% CI: 0.84-1.23) and suicide mortality (aHR=0.81, 95% CI: 0.52-1.26).

The results of the sensitivity analyses among first-episode patients were consistent with primary analyses (clozapine monotherapy: aHR=0.42, 95% CI: 0.30-0.59 for all-cause mortality, and aHR=0.46, 95% CI: 0.19-1.09 for cardiovascular mortality). In the comparison between any LAI versus an equivalent oral antipsychotic, they were associated with similar mortality risk (aHR=1.00, 95% CI: 0.93-1.07). Analyses of all-cause mortality in the prevalent cohort without censoring to >7 days hospitalizations yielded similar results as with censoring.

In sensitivity analysis excluding the first 10 years of follow-up, the most favorable outcome for all-cause mortality was observed with LAI olanzapine (aHR=0.13, 95% CI: 0.03-0.53) and oral flupentixol (aHR=0.36, 95% CI: 0.16-0.81), whereas clozapine ranked as 7th among the 19 most frequently used antipsychotics (aHR=0.47, 95% CI: 0.41-0.54).

The results of sensitivity analyses with a nested case-control design on associations between cumulative antipsychotic exposure and all-cause and cardiovascular mortality were also consistent with the primary analyses. Compared with non-use of antipsychotics, use for ≥80% of outpatient observation time was associated with a decreased risk of all-cause mortality (adjusted odds ratio, aOR=0.73, 95% CI: 0.60-0.88). For cardiovascular mortality, antipsychotic use was also associated with a decreased risk, but confidence intervals were wide, resulting in non-significant findings (aOR=0.80, 95% CI: 0.57-1.12). Results for clozapine use were similar to those for any antipsychotic use, concerning both all-cause mortality (aOR=0.61, 95% CI: 0.44-0.86) and cardiovascular mortality (aOR=0.54, 95% CI: 0.21-1.39).

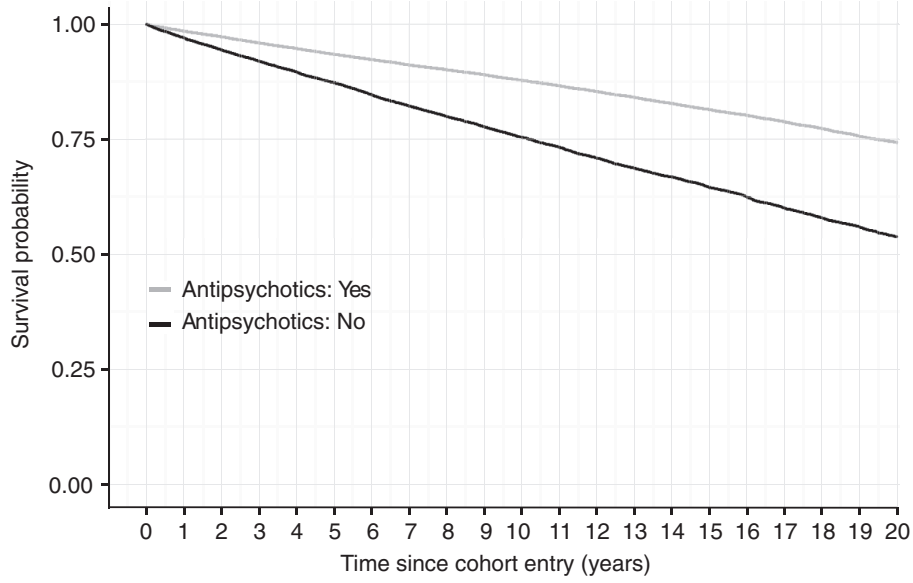

Figure 3 All-cause mortality in patients using any antipsychotic versus those who used none in the prevalent cohort

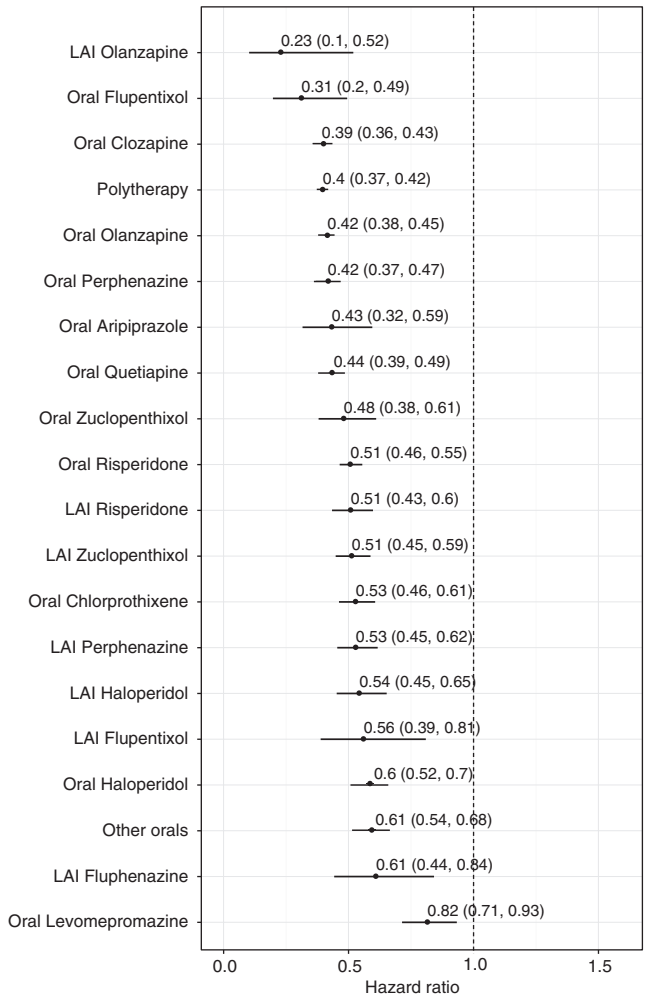

Figure 4 All-cause mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

DISCUSSION

In this non-randomized, observational, nationwide sample with up to 20 years of follow-up (median 14.1 years), we found that antipsychotic use was not associated with an increased risk of hospitalization due to somatic or cardiovascular reasons in patients with schizophrenia. Furthermore, antipsychotic use was associated with a decreased risk of all-cause, cardiovascular and suicide mortality, also in terms of cumulative antipsychotic exposure. Among specific antipsychotics, clozapine was associated with the most beneficial outcome concerning reduced mortality.

Our results on the association between antipsychotic use and mortality are consistent with previous observational studies[19-22,27]. However, the present investigation uniquely adds to the literature with the largest cohort ever, allowing meaningful analyses regarding specific antipsychotics, plus truly long-term follow-up of up to 20 years compared with 5-11 years in previous studies. Thus, we were able to assess longer-term outcomes, which is important due to the life-long duration of schizophrenia and the occurrence of adverse events as a function of long-term cumulative exposure.

Regarding physical morbidity, periods of antipsychotic use were not associated with an increased risk of somatic or cardiovascular hospitalizations. These findings on long-term outcomes may appear inconsistent with the adverse effects of short-term antipsychotic use, including weight gain and obesity, impaired glucose tolerance, dyslipidemias and cardiovascular events, which are all intermediate risk factors for cardiovascular morbidity and mortality[9,11,12,14]. An explanation for this disconnect is likely to be the improved control of psychiatric symptoms associated with antipsychotic use, which in turn may lead to improved adherence to healthy lifestyle behaviors and utilization of health care services for physical illnesses[13].

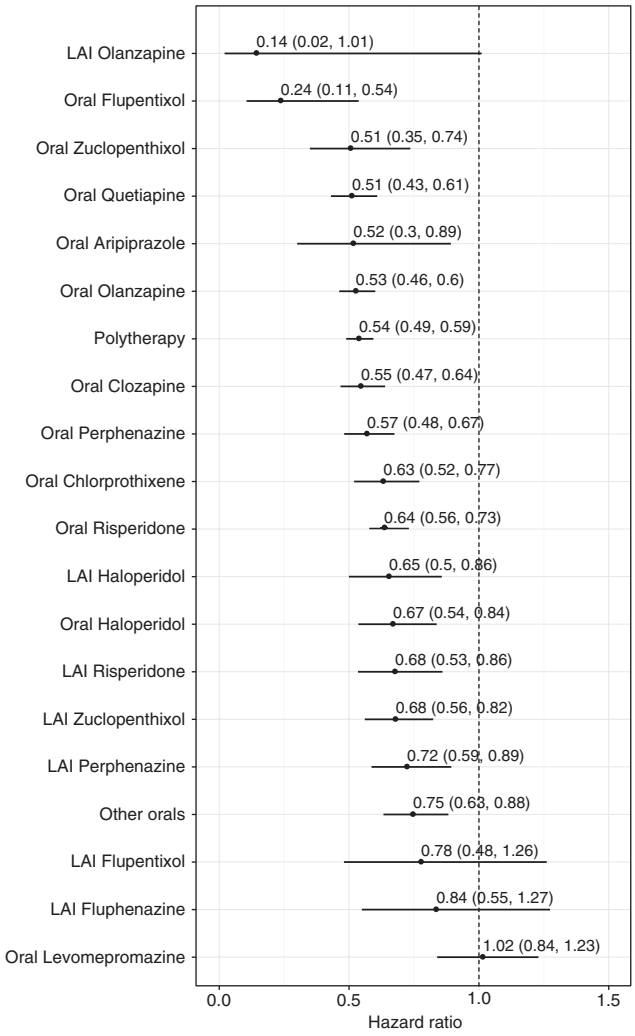

Figure 5 Cardiovascular mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

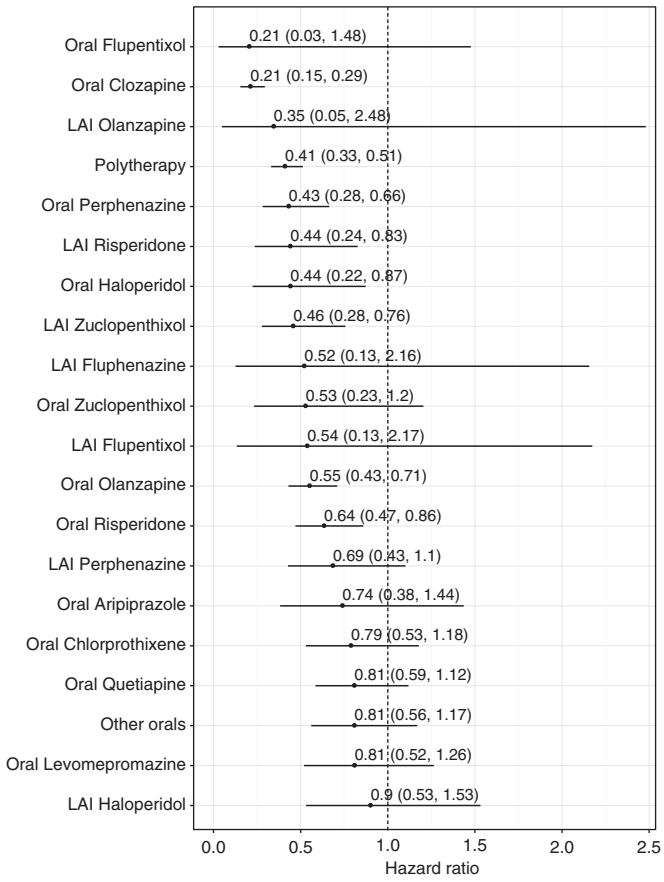

Figure 6 Suicide mortality in patients receiving monotherapy with specific antipsychotics compared to those who received none in the prevalent cohort with censoring to >7 days hospitalizations (adjusted hazard ratios with 95% CIs). LAI – long-acting injectable

Persons with schizophrenia have a greater prevalence of sedentary lifestyle, obesity and smoking[6,28,29], are less likely to receive adequate pharmacotherapy for hypertension and dyslipidemias[30,31], and are seldom tested for glucose and lipid alterations[32,33]. This problematic general reduction in adequate secondary prevention of cardiovascular morbidity and mortality is likely aggravated in individuals with schizophrenia not taking antipsychotics.

There are several other possible mechanisms explaining the decreased mortality in patients receiving antipsychotic treatment. Antipsychotics reduce symptoms of schizophrenia, and this may be a major factor for decreased suicide mortality[20]. Relief of stress may also have a beneficial effect on cardiovascular mortality. Smoking and high blood pressure are among the most important risk factors for cardiovascular death[34], and antipsychotics, especially clozapine, decrease blood pressure and possibly also the rate of smoking[35,36].

The results of our study are consistent with previous results from Sweden[21]. However, some differences in the comparative effectiveness of specific antipsychotics emerged. In the Swedish study, LAIs were associated with a 33% lower risk of all-cause mortality compared with equivalent oral antipsychotics[21], while in the current study no significant difference between LAIs and oral antipsychotics was observed. The superiority of LAIs in Sweden may be related to the fact that those preparations were used more frequently (29% of all antipsychotic use person-years) during the observation period in that country (2006-2013)[21], compared to this study in Finland (8.5% of antipsychotic use person-years in the period 1996-2015).

We found that clozapine was associated with the lowest mortality, in line with the meta-analysis by Vermeulen et al[37], which reported that continuous clozapine treatment is associated with an about 40% lower all-cause mortality compared to other antipsychotics. Clozapine is recommended for use after two other antipsychotics have been ineffective[38] and, therefore, is generally initiated later in the illness course than other antipsychotics. Since mortality may be particularly high in the early phase of the illness[39], the later use of clozapine could introduce a survival bias. Therefore, we conducted sensitivity analyses by excluding the first ten years of follow-up. In these analyses, clozapine was indeed associated with a slightly lower comparative effectiveness, ranking as 7th among the 19 most frequently used antipsychotics in monotherapy. This finding suggests that survival bias related to early phase mortality may affect the rank order of antipsychotics to some extent.

To our knowledge, this is the largest cohort with the longest follow-up to study morbidity and mortality during antipsychotic treatment in people with schizophrenia or any diagnosis. The results may be particularly generalizable to countries with a state-funded health care system, where antipsychotics are provided for patients with no or very small co-payments. Antipsychotic use was modelled with the PRE2DUP method[24], which produces reliable estimates of drug exposure and performs better than other previously used modelling methods for register-based data[40].

Hospitalization-based outcomes were analyzed by within-individual analyses. All time-invariant factors are controlled for in this design, which therefore is superior to other analyses in adjusting for fixed and even unmeasured characteristics such as diet, exercise and genetic factors. The underlying severity of disease is also controlled for in this design, which is an advantage over traditional observational studies, and the impact of co-medications was adjusted for.

One theoretical source of bias is that a patient may experience a side effect and discontinue medication, be hospitalized a few days or weeks later, and counted as a non-user of antipsychotic drugs. However, in Finland, each prescription dispensing lasts typically 90 days. The exact timing of discontinuation of use is not known, and drug use modelling assumes that all medications dispensed are used. In addition, the utilized modelling method adds some days of extra duration after the calculated antipsychotic drug use has ended, in order to ensure that the end of drug use is correctly assigned if some down-titration happens after long drug use. These design features ensure that rapid antipsychotic discontinuations provoked by adverse effects are assigned to the antipsychotic exposure instead of non-exposure period, and that no major misclassification of "past users" occurs.

Mortality analyses were traditional between-individual models and were adjusted for comorbid conditions associated with survival. The analyses were also adjusted for time-dependent use of other medications, which aimed at better control for emergence and progression of the comorbid conditions during long follow-up. Temporal order of antipsychotics was adjusted for in all analysis, by taking into account that clozapine is initiated later. Sensitivity analyses aimed at analyzing possible sources of bias, and the results of these analyses did not change the overall interpretation of data.

As in all observational studies, residual confounding may exist, especially in between-individual analyses. We lacked information on important lifestyle behaviors, such as smoking and diet. Somatic comorbidities were based only on diagnoses in hospital care and were, therefore, likely under-reported. The impact of this potential bias was reduced by updating data on comorbid conditions in a time-dependent fashion in the between-individual analyses. Survival bias related to prevalent cases was reduced by conducting analyses separately among incident cases, and the results were similar, although the sample size and number of deaths was reduced, which limited statistical power.

In conclusion, in this nationwide observational study, long-term antipsychotic use was not associated with increased severe physical morbidity among persons with schizophrenia when comparing exposure and non-exposure periods in the same person. In addition, compared to no antipsychotic use, long-term antipsychotic use was associated with substantially lower all-cause, cardiovascular and suicide mortality in people with schizophrenia. These results indicate that excess mortality in schizophrenia may not be attributable to antipsychotics, but at least partially and to a relevant degree to non-use of antipsychotics.

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Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial

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Antipsychotics are used for many psychiatric conditions in youth. Although developmentally inappropriate weight gain and metabolic abnormalities, which are risk factors for premature cardiovascular mortality, are especially frequent in youth, optimal strategies to reduce pediatric antipsychotic-induced overweight/obesity are unclear. The Improving Metabolic Parameters in Antipsychotic Child Treatment (IMPACT) was a randomized, parallel group, 24-week clinical trial which enrolled overweight/obese, psychiatrically stable youth, aged 8-19 years, with a DSM-IV diagnosis of severe mental illness (schizophrenia spectrum disorder, bipolar spectrum disorder or psychotic depression), at four US universities. All of them had developed substantial weight gain following treatment with a second-generation antipsychotic. The centralized, computer-based randomization system assigned participants to unmasked treatment groups: metformin (MET); antipsychotic switch (aripiprazole or, if already exposed to that drug, perphenazine or molindone; SWITCH); or continued baseline antipsychotic (CONTROL). All participants received healthy lifestyle education. The primary outcome was body mass index (BMI) z-score change from baseline, analyzed using estimated least squares means. Altogether, 127 participants were randomized: 49 to MET, 31 to SWITCH, and 47 to CONTROL. BMI z-score decreased significantly with MET (week 24: –0.09±0.03, p=0.002) and SWITCH (week 24: –0.11±0.04, p=0.003), while it increased non-significantly with CONTROL (week 24: +0.04±0.03). On 3-way comparison, BMI z-score changes differed significantly (p=0.001). MET and SWITCH were each superior to CONTROL (p=0.002), with effect sizes of 0.68 and 0.81 respectively, while MET and SWITCH did not differ. More gastrointestinal problems occurred in MET than in SWITCH or CONTROL. The data safety monitoring board closed the perphenazine-SWITCH arm because 35.2% of subjects discontinued treatment due to psychiatric worsening. These data suggest that pediatric antipsychotic-related overweight/obesity can be reduced by adding metformin or switching to a lower risk antipsychotic. Healthy lifestyle education is not sufficient to prevent ongoing BMI z-score increase.

Key words: Antipsychotics, weight gain, youth, obesity, metformin, antipsychotic switch, healthy lifestyle education, IMPACT

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Antipsychotics are commonly used to treat many different mental disorders[1] and are frequently associated with weight gain and metabolic abnormalities[2-4], particularly in children and adolescents[4-7], which increases the risk for premature mortality[8]. Cardiometabolic risk monitoring in antipsychotic-treated patients is often inadequate[9,10], especially in youth[11-13]. Interventions for antipsychotic-related weight gain and metabolic abnormalities are still insufficiently established and, especially, infrequently implemented[14,15].

The Harvard Growth Study found that being overweight in adolescence is a more significant predictor of morbidity from coronary heart disease than being overweight as an adult[16]. A large population cohort study reported that adult coronary heart disease was positively associated with body mass index (BMI) at age 7-13 for boys and 11-13 for girls, with the risk increasing across the entire BMI distribution[17]. So, overweight/obesity induced by antipsychotic treatment in youth is a major public health concern.

Several strategies to reduce antipsychotic-induced weight gain have been tested in adults[14]. They include behavioral lifestyle interventions[18], switch to a lower-risk antipsychotic[19], and addition of topiramate[20] or metformin[21].

In adults, results of behavioral interventions have been mixed. A large randomized controlled trial (RCT) failed to show significant benefit[22]. A recent meta-analysis[18] of 41 RCTs (N=4,267) showed that, in adults with severe mental illness, individualized healthy lifestyle interventions lasting on average 22 weeks were able to reduce BMI by 0.63 kg/m^2 compared to control groups. However, after an average of 32 weeks post-intervention, the effect size remained similar in 17 RCTs, but was no longer significant. Most studies had very low or low quality of evidence, and the statistically significant effects were considered very likely not to be clinically significant[18].

In contrast to these data available in adults, there are almost no RCTs of behavioral weight reduction programs for children and adolescents with antipsychotic-related weight gain. The only pediatric RCT of a 52-week behavioral weight counseling intervention in adolescents with schizophrenia or bipolar disorder failed to demonstrate significant benefits[23].

Among the pharmacological weight loss interventions for adults with severe mental illness, metformin is so far the best studied[14,21]. In a meta-analysis of 19 RCTs (N=1,279), the addition of metformin to antipsychotic treatment for an average of 3-4 months significantly reduced body weight relative to control

conditions, with a medium effect size of 0.61[21].

The mechanism for weight loss induced by metformin is not entirely clear, but data suggest a variety of effects[24]. It has been well documented that metformin decreases hepatic gluconeogenesis and improves insulin sensitivity in the liver and muscle. Because insulin levels are elevated as part of insulin resistance following non-physiologic weight gain, and insulin increases appetite, improvement of insulin resistance by metformin could reduce appetite and caloric intake. Additionally, metformin has been shown to affect hypothalamic signaling, regulating leptin sensitivity, gastrointestinal physiology and circadian rhythms, which may not only influence food intake, but also fat oxidation and fat storage in liver, skeletal muscle, and adipose tissue[24].

Data on pharmacological interventions aimed at weight reduction in youth with antipsychotic-induced overweight/obesity are far more limited than in adults. Only three RCTs of metformin are available, lasting 12 to 16 weeks[25-27]. In a study of 39 youth with mixed psychiatric disorders, metformin separated from placebo on anthropometric, but not metabolic parameters[25]. In a trial of 49 youth with schizophrenia spectrum disorders, differences favoring metformin treatment were not statistically significant for body weight parameters, and no trends toward metabolic benefits were evident[26]. In a study of 60 youth with autism, metformin separated from placebo on anthropometric, but not on metabolic measures[27].

Moreover, no pediatric or adult RCT to date has directly compared the effects of antipsychotic switching versus add-on of a weight loss agent, and no pediatric trial has examined combined medication and behavioral treatment.

The objective of this study was to compare the efficacy and tolerability of the addition of metformin, the switch to an antipsychotic with lower risk for weight gain, and continued antipsychotic treatment, against the background of healthy lifestyle education (HLE), in youth with severe mental illness and clinically significant antipsychotic-induced weight gain.

METHODS

The Improving Metabolic Parameters in Antipsychotic Child Treatment (IMPACT) was a randomized, unmasked parallel group clinical trial, approved and monitored by the Institutional Review Boards at Zucker/Hillside Hospital, Johns Hopkins University, University of Maryland, and University of North Carolina at Chapel Hill[28]. It was funded by the US National Institute of Mental Health (NIMH).

Participants

Youth aged 8-19 years were enrolled for the study if they had a primary DSM-IV diagnosis of schizophrenia spectrum disorder, bipolar spectrum disorder, or major depression with psychotic features. Psychiatric diagnoses were established at the screening appointment using the Leibenluft modification of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime version (K-SADS-PL)[29,30].

Further inclusion criteria were: a) having been treated with a second-generation antipsychotic (SGA) – aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone or ziprasidone – with a stable dose for at least 30 days; b) having been clinically stable on current treatment regimen, as assessed by Clinical Global Impression - Severity and Improvement (CGI-I and CGI-S)[31], for at least 30 days; c) having a BMI ≥85th percentile for age and gender (i.e., being overweight or obese); d) having had a substantial weight gain (>10% baseline weight) while taking the SGA; e) having a primary caretaker (parent(s), close relative functioning *in loco parentis*, legal guardian, or foster parent) who had known the person for at least 6 months before study entry; f) being able to participate in all aspects of the protocol per investigator clinical judgment.

Exclusion criteria were: a) treatment with more than one antipsychotic medication, or more than three total psychiatric medications (four were permitted if two were for attention-deficit/hyperactivity disorder (ADHD)); b) antipsychotic treatment with clozapine (which is exclusively used for treatment-refractory illness); c) psychiatric medication or dosage change within the past 30 days; d) any medication affecting glucose, insulin or lipid levels; d) any major neurological or medical illness affecting body weight or physical activity; e) abnormal fasting glucose (≥126 mg/dL) or serum creatinine (>1.3 mg/dL); f) substance dependence disorder (except tobacco dependence) in the past month; g) current or lifetime diagnosis or anorexia or bulimia nervosa; h) IQ <55; i) known hypersensitivity to aripiprazole, perphenazine or metformin; j) prior trials with aripiprazole or perphenazine lasting more than 2 weeks and stopped because of efficacy or tolerability concerns; k) significant risk of dangerousness to self or other; l) for female participants, pregnant, nursing or sexually active and unwilling to comply with double method contraceptive. ADHD medications and valproate were permitted.

Procedures

All 18-19 year-old participants and at least one parent of minors provided written informed consent; all participants <18 years old provided assent. Eligibility was determined based on a 3-week screening period to establish psychiatric and physical health status and stability.

All eligible youth received HLE and were randomized to 24 weeks of open-label treatment with either: a) add-on metformin (MET); b) switch of SGA to a lower cardiometabolic risk antipsychotic (aripiprazole or, if previously exposed to this drug, molindone – prior to its removal from the US market – or perphenazine) (SWITCH); c) continued treatment with the current SGA (CONTROL). All metformin-treated youth were given a daily multi-vitamin, to prevent vitamin B12 deficiency[32].

Molindone was originally chosen for the SWITCH condition when patients presented with significant weight gain while being on aripiprazole. It was selected as it produced the least weight

gain in the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS)[33] study. When it became unavailable in the US, the NIMH strongly recommended retaining the comparison between a SGA (aripiprazole) and a first-generation antipsychotic (FGA) in the SWITCH arm. Among available FGAs, we chose perphenazine, as it had a better profile in terms of weight gain and metabolic changes than SGAs in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project[34].

Randomizations were performed through a centralized, computer-based system. They were stratified for current SGA (risperidone, aripiprazole or "other antipsychotic") and diagnosis (schizophrenia spectrum or other disorder). Patients, caregivers and study team members learned about the randomization assignment at the end of the baseline visit.

All study conditions involved 10 in-person visits (at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 weeks) and 6 phone sessions (at 3, 5, 7, 9, 10 and 11 weeks). Metabolic assessments were performed at baseline, 12 weeks and 24 weeks.

Psychiatric symptomatology was assessed at baseline and at weeks 12 and 24 by independent evaluators (physicians with ≥2 years of experience working with psychiatrically ill youth), blind to study condition and medication adverse events, using the 21-item Brief Psychiatric Rating Scale for Children (BPRS-C)[35].

Ongoing monitoring during the treatment phase included review of psychiatric symptoms, adverse events and medication adherence by board-certified child and adolescent psychiatrists. Review of psychiatric symptoms was done using the CGI-I and CGI-S. Adverse events were assessed by the Systematic Longitudinal Adverse Event Scale (SLAES)[36], the Simpson-Angus Extrapyramidal Symptoms Scale (SAEPS)[37], the Barnes Akathisia Rating Scale (BARS)[38] and the Abnormal Involuntary Movement Scale (AIMS)[39].

All metabolic laboratory values at the main visits (baseline, 12 weeks, and 24 weeks) were obtained after an overnight fast of at least 8 hours. Glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, homeostatic model assessment for insulin resistance (HOMA-IR), hemoglobin A1c (HgbA1c), and C-reactive protein were measured.

For all cases, parent/patient self-report adherence data were obtained regarding all psychotropic medications. For all participants receiving study medications (i.e., switch antipsychotic or metformin), information was also collected by pill count at all appointments. For all patients, antipsychotic blood levels were measured at weeks 12 and 24.

Patients could be withdrawn from the study and referred for clinical care based on either: a) participant or guardian request, b) judgment of the independent pediatrician or consulting pediatric endocrinologist that metabolic problems required treatment outside of the study, or c) significant worsening of psychiatric symptoms operationalized as a CGI-I rating of "much worse" or "very much worse" on two successive occasions over a period of ≥2 weeks.

Youth might also be withdrawn if moderate/severe adverse events occurred that could not be addressed by dose adjustment or addition of permitted concomitant four medications or, if requested by the site principal investigator, due to non-compliance or clinical status.

Treatment conditions

HLE consisted of education about strategies to enhance nutrition and physical activity, as well as regular weight monitoring[40]. The frequency of visits increased if participants gained 5% and 10% of baseline body weight.

For youth weighing <50 kg, the metformin titration started with 250 mg taken with dinner, which was increased by 250 mg (taken at breakfast) after 1 week, and subsequently by 250 mg steps on a weekly basis (taken twice daily, with breakfast and dinner), until 500 mg twice daily was reached. For youth weighing 50-70 kg, the maximum metformin dose was 500 mg in the morning and 1,000 mg in the evening.

For youth weighing >70 kg, the metformin titration started with 500 mg taken with dinner, which was increased by 500 mg (taken at breakfast) after 1 week, and subsequently by 500 mg steps on a weekly basis (taken twice daily, with breakfast and dinner), until 1,000 mg twice daily was reached.

During the plateau cross-titration from the baseline SGA to either aripiprazole or perphenazine, the baseline SGA was kept at the same dose for 3 weeks, and then tapered by 25% of the baseline dose over the next 3 weeks. Aripiprazole was initiated at 2 mg/day for one week, increased to 5 mg/day at week 2, and then increased in 5 mg steps to a maximum of 30 mg/day. Perphenazine was initiated at 4 mg/day and increased weekly by 4 mg to a maximum of 64 mg/day.

Both the metformin titration speed and SGA cross-titration could be altered based on clinical response. In perphenazine-SWITCH, benztropine 0.5 mg bid was required when perphenazine reached >8 mg/day. Metformin-XR could be used if intolerable gastrointestinal problems occurred.

Outcomes

The primary outcome was BMI z-score change. BMI z-scores were calculated using the program provided by the Children's Nutrition Research Center at Baylor College of Medicine. Secondary outcomes included changes in other anthropometric measures, glucose and lipid parameters, C-reactive protein, and the child-rated Impact of Weight on Quality of Life-Kids (IWQOL-Kids)[41].

Safety outcomes included longitudinal review of adverse effects elicited using the SLAES, SAEPS, BARS and AIMS, and psychiatric assessment by blinded raters using the CGI-I and BPRS-C.

Statistical analyses

Efficacy outcomes from subjects with baseline and ≥1 post-baseline value were analyzed using a longitudinal mixed model

entering predictors for treatment, visit (treated as a categorical variable with an unstructured covariance pattern to reflect correlation between each subject's visits), treatment-by-visit interaction, and baseline score into the model. Least squares means (LSMs) for change from baseline were estimated at each visit for each treatment group and for differences between each pair of treatment groups. LSMs are only reported from weeks 12 and 24, but models were fit using data from all available time points. All hypothesis-testing analyses used a hierarchical approach to preserve power and eliminate inflation of the overall experiment-wise error rate.

Imputation due to early termination was limited to variables collected only at week 12 and week 24. Discontinuation data from weeks 1-11 was carried-forward to week 12; data from weeks 13-23 to week 24. Kenward-Roger degrees of freedom[42] were used in the denominator of significance tests to correct for multiple comparisons.

Time to discontinuation was estimated using Kaplan-Meier survival curve with log-rank tests to compare treatment groups. Demographics, adverse events, and other safety variables were summarized using basic descriptive statistics. Exploratory *post-hoc* chi-squared analyses compared the three groups for categorical weight gain and incidence of adverse events without multiple comparisons corrections.

Based on a power calculation, a sample size of 44 per group (total N=132) yielded 80% power to detect a significant difference regarding the primary outcome, BMI z-score.

RESULTS

Participants

Between October 2009 and October 2013, 127 subjects were randomized (CONTROL=47; MET=49; SWITCH=31). Adverse event analyses excluded five participants (CONTROL=2, MET=2, SWITCH=1), who discontinued without providing adverse event information after learning their randomization assignment. Primary efficacy analyses included 121 participants (CONTROL=44; MET=47; SWITCH=30: aripiprazole=12, perphenazine=17; molindone =1) with ≥1 post-baseline vital sign measurement.

Baseline characteristics

Patients' baseline demographic and clinical characteristics are summarized in Table 1. Mean age was 13.7±3.3 years, 64.6% were male, and 52.7% were White. Primary diagnoses were bipolar spectrum disorder in 84.2% of patients, schizophrenia spectrum disorder in 9.4% and psychotic depression in 6.3%. The most common comorbid diagnoses were ADHD (35.4%), autism spectrum disorder (26.0%), anxiety disorders (25.2%), and oppositional defiant disorder or conduct disorder (21.2%). Among the participants, 52.0% had had prior psychiatric hospitalizations.

Aripiprazole (46.4%) and risperidone (38.6%) were the most frequently antipsychotics received at baseline. Mean durations of current and total antipsychotic use were 21.6±20.4 and 29.9±23.1 months, respectively. Almost half (43.3%) had been treated consecutively with multiple antipsychotics. Treatment groups did not differ significantly on anthropometric, psychiatric and metabolic parameters at baseline.

Treatment

Most (72.3%) participants achieved their targeted MET dose by week 12. One additional participant achieved it by week 24. Mean endpoint metformin doses were 1,000±500 mg/day for youth weighing <50 kg; 1,250±500 mg/day for those weighing 50-70 kg, and 1,766±442 mg/day for those weighing >70 kg.

Ten (83.3%) participants switching to aripiprazole did so by week 8; one was unable to completely discontinue his baseline SGA. Of those switching to perphenazine, 58.8% did so by week 8; 41.2% were unable to discontinue their baseline SGA. Mean endpoint doses were 12.8±9.0 mg/day for aripiprazole and 11.6±10.2 mg/day for perphenazine. Other psychotropics remained virtually unchanged throughout the study.

Mean treatment duration was 19.4±8.4 weeks for CONTROL, 20.3±7.2 weeks for MET, and 18.2±8.3 weeks for SWITCH (p=0.113), with marked discrepancy between aripiprazole (20.6 ±8.3 weeks), perphenazine (16.9±8.0 weeks) and molindone (12 weeks).

All-cause discontinuation was significantly greater in perphenazine-SWITCH (52.9%) than any other group (p=0.041; CONTROL=25.5%, MET=21.2%, SWITCH=36.6%, aripiprazole-SWITCH=8.3%), primarily due to inadequate psychiatric efficacy (p=0.0014, CONTROL=6.3%, MET=4.1%, aripiprazole-SWITCH=0%, perphenazine-SWITCH=35.2%). Consequently, the NIMH data safety monitoring board closed the perphenazine-SWITCH arm on February 8, 2013.

Primary outcome

Table 2 shows estimated changes from baseline to endpoint, p values and effect sizes for within-group changes, the 3-way comparison, and, if this comparison was significant, pairwise-group comparisons for all efficacy outcomes.

The BMI z-score decreased significantly in both MET (week 12: –0.03±0.01, p=0.019; week 24: –0.09±0.03, p=0.002) and SWITCH (week 12: –0.05±0.02, p=0.008, week 24: –0.11±0.04, p=0.003), while it increased non-significantly in CONTROL (week 12: +0.03 ±0.01, week 24: +0.04±0.03).

The BMI z-score change differed significantly between the three groups at weeks 12 (p=0.002) and 24 (p=0.001), with both MET (p=0.005 and p=0.002, respectively) and SWITCH (p=0.002 at both times) superior to CONTROL, with effect sizes from 0.40 to 0.81 and no significant difference between MET and SWITCH (Table 2 and Figure 1).

Table 1 Demographic and clinical characteristics of the study participants at baseline (randomized population)

	Control (N=47)	Metformin (N=49)	Switch (N=31)	Total (N=127)
Age (mean±SD)	13.4±3.2	13.4±3.2	14.7±3.3	13.7±3.3
8-12 years (%)	51.1	44.9	29.0	43.3
13-17 years (%)	36.2	46.9	54.8	44.9
18+ years (%)	12.8	8.2	16.1	11.8
Gender (% males)	63.8	63.3	67.7	64.6
Ethnicity (%)				
White	53.2	53.1	51.6	52.7
Black	27.6	28.6	29.0	28.3
Other	19.1	18.4	19.3	18.9
Primary psychiatric diagnosis (%)				
Schizophrenia spectrum disorder	10.6	12.2	3.2	9.4
Bipolar spectrum disorder	83.0	83.7	22.6	84.2
Psychotic depression	6.4	4.1	9.7	6.3
Main comorbid diagnoses (%)				
ADHD	31.9	34.7	41.9	35.4
Autism spectrum disorder	29.8	28.6	16.1	26.0
Anxiety disorders	29.8	28.6	12.9	25.2
Oppositional defiant disorder/conduct disorder	19.1	20.4	25.8	21.2
Antipsychotic medication at baseline (%)				
Aripiprazole	51.1	40.8	48.4	46.4
Risperidone	36.2	40.8	38.7	38.6
Ziprasidone	8.5	8.2	6.4	7.9
Olanzapine	2.1	6.1	3.2	3.9
Quetiapine	2.1	4.1	3.2	3.1
Psychiatric co-medication at baseline (%)				
Psychostimulant	40.4	44.9	41.9	42.5
Antidepressant	34.0	36.7	38.7	36.2
Mood stabilizer	19.1	26.5	12.9	20.5
Non-stimulant anti-ADHD medication	31.9	4.1	12.9	16.5
Hypnotic/anxiolytic	12.8	18.4	19.3	16.5
Anticholinergic	10.6	8.2	6.4	8.7
Current antipsychotic use (months, mean±SD)	22.7±18.5	21.6±23.2	19.8±18.4	21.6±20.4
Total antipsychotic use (months, mean±SD)	30.8±20.9	29.0±26.7	30.0±20.3	29.9±23.1
Treated with multiple consecutive antipsychotics (%)	40.4	61.2	51.6	43.3
Prior psychiatric hospitalizations (%)	44.7	53.1	61.3	52.0

ADHD – attention-deficit/hyperactivity disorder

Secondary anthropometric outcomes

All other anthropometric measures followed the same pattern as the primary outcome (Table 2). Weight increased significantly in CONTROL (week 12: +4.3±0.8 lbs, p<0.0001; week 24: +8.5±1.5 lbs, p<0.001), while remaining essentially the same in MET (+0.3±0.7 lbs and –0.4±1.4 lbs) and SWITCH (+0.3±0.9 lbs and +0.3±1.9 lbs). The 3-way comparison was significant at week 12 (p=0.0002) and 24 (p<0.0001), with both MET and SWITCH outperforming CONTROL at both times (effect size from 0.66 to 0.99).

Weight loss occurred in 55.1% of MET, 46.7% of SWITCH and

Table 2 Change from baseline to week 12 and to week 24 in anthropometric, metabolic and psychiatric outcomes (efficacy population)

	Control, within group (N=44)			Metformin, within group (N=47)			Switch, within group (N=30)			3-way comparison	Control vs. Metformin		Control vs. Switch		Metformin vs. Switch	
	LSM (SE)	p	ES	LSM (SE)	p	ES	LSM (SE)	p	ES	p	p	ES	p	ES	p	ES
BMI z-score																
Week 12	0.03 (0.01)	NS	0.05	–0.03 (0.01)	0.019	–0.07	–0.05 (0.02)	0.008	–0.10	0.002	0.005	0.40	0.002	0.51	NS	0.11
Week 24	0.04 (0.03)	NS	0.08	–0.09 (0.03)	0.002	–0.18	–0.11 (0.04)	0.003	–0.23	0.001	0.002	0.68	0.002	0.81	NS	0.13
Fasting insulin (μU/mL)																
Week 12	–15.3 (11.3)	NS	–0.15	–33.0 (10.3)	0.002	–0.33	–5.7 (14.2)	NS	–0.06	NS		0.31		–0.17		–0.48
Week 24	17.4 (20.1)	NS	0.17	–18.6 (16.4)	NS	–0.18	4.4 (23.0)	NS	0.04	NS		0.42		0.15		–0.27
Weight (lbs)																
Week 12	4.3 (0.8)	<0.0001	0.07	0.3 (0.7)	NS	0.00	0.3 (0.9)	NS	0.01	0.0002	0.0002	0.67	0.001	0.66	NS	–0.01
Week 24	8.5 (1.5)	<0.001	0.14	–0.4 (1.4)	NS	–0.01	0.3 (1.9)	NS	0.01	<0.0001	<0.0001	0.99	0.0008	0.91	NS	–0.08
BMI percentile																
Week 12	0.5 (0.2)	0.017	0.12	–0.1 (0.2)	NS	–0.03	–0.4 (0.2)	NS	–0.09	0.016	0.029	0.22	0.008	0.31	NS	0.10
Week 24	0.7 (0.4)	0.045	0.19	–0.5 (0.4)	NS	–0.13	–0.9 (0.5)	0.054	–0.23	0.01	0.015	0.40	0.006	0.54	NS	0.13
Fasting glucose (mg/dL)																
Week 12	3.1 (1.8)	NS	0.27	–6.1 (1.5)	0.0002	–0.53	–2.8 (2.1)	NS	–0.24	0.001	0.0002	0.95	0.036	0.62	NS	–0.34
Week 24	0.9 (2.0)	NS	0.08	–0.3 (1.7)	NS	–0.03	0.7 (2.6)	NS	0.06	NS		0.12		0.02		–0.10
HOMA-IR																
Week 12	–0.29 (0.41)	NS	–0.08	–1.43 (0.36)	0.0002	–0.4	–0.31 (0.50)	NS	–0.09	NS		0.57		0.01		–0.56
Week 24	0.63 (0.82)	NS	0.17	–0.46 (0.65)	NS	–0.13	0.30 (0.91)	NS	0.08	NS		0.33		0.10		–0.23
HbA1c (%)																
Week 12	0.00 (0.04)	NS	0.00	–0.05 (0.03)	NS	–0.15	–0.03 (0.04)	NS	–0.10	NS		0.23		0.15		–0.08
Week 24	0.02 (0.04)	NS	0.05	–0.09 (0.04)	0.028	–0.27	0.01 (0.06)	NS	0.04	NS		0.43		0.01		–0.42
Total cholesterol (mg/dL)																
Week 12	3.5 (4.0)	NS	0.11	–6.6 (3.8)	NS	–0.20	–1.9 (4.7)	NS	–0.06	NS		0.41		0.22		–0.19
Week 24	5.3 (4.4)	NS	0.16	–1.2 (4.2)	NS	–0.04	–10.2 (5.7)	NS	–0.31	NS		0.25		0.59		0.34
HDL-cholesterol (mg/dL)																
Week 12	0.7 (1.6)	NS	0.06	1.0 (1.5)	NS	0.08	–2.5 (1.9)	NS	–0.20	NS		–0.02		0.33		0.35
Week 24	0.4 (1.1)	NS	0.04	–0.1 (1.1)	NS	–0.01	–3.9 (1.5)	0.009	–0.31	NS		0.09		0.65		0.57
LDL-cholesterol (mg/dL)																
Week 12	2.6 (3.6)	NS	0.10	–6.0 (3.3)	NS	–0.22	2.2 (4.2)	NS	0.08	NS		0.39		0.02		–0.37
Week 24	3.6 (4.1)	NS	0.13	–3.9 (3.9)	NS	–0.14	–8.3 (5.3)	NS	–0.30	NS		0.31		0.49		0.18

Table 2 Change from baseline to week 12 and to week 24 in anthropometric, metabolic and psychiatric outcomes (efficacy population) *(continued)*

	Control, within group (N=44)			Metformin, within group (N=47)			Switch, within group (N=30)			3-way comparison	Control vs. Metformin		Control vs. Switch		Metformin vs. Switch	
	LSM (SE)	p	ES	LSM (SE)	p	ES	LSM (SE)	p	ES	p	p	ES	p	ES	p	ES
Triglycerides (mg/dL)																
Week 12	–5.8 (6.6)	NS	–0.10	–7.2 (6.2)	NS	–0.12	–6.6 (7.7)	NS	–0.11	NS		0.03		0.02		–0.01
Week 24	0.2 (9.1)	NS	0.00	14.7 (8.7)	NS	0.25	16.6 (12.0)	NS	0.28	NS		–0.27		–0.30		–0.04
C-reactive protein (mg/L)																
Week 12	0.07 (0.75)	NS	0.02	–0.52 (0.69)	NS	–0.13	–0.63 (1.09)	NS	–0.15	NS		0.16		0.19		0.03
Week 24	0.87 (0.82)	NS	0.21	–0.86 (0.77)	NS	–0.21	–1.64 (1.26)	NS	–0.39	NS		0.46		0.66		0.21
CGI severity score																
Last – baseline	0.28 (0.78)	NS		–0.04 (0.86)	NS		–0.12 (1.11)	NS		NS						
CGI improvement score																
Last	3.38 (1.03)			3.43 (1.15)			3.80 (1.35)			NS						
BPRS-C total score																
Week 12	–3.1 (1.7)	NS	–0.22	–2.8 (1.6)	NS	–0.20	–6.5 (2.1)	0.002	–0.45	NS		–0.03		0.31		0.34
Week 24	–4.3 (1.7)	0.012	–0.30	–4.6 (1.6)	0.006	–0.32	–4.8 (2.2)	0.031	–0.34	NS		0.03		0.05		0.02
IWQOL-Kids physical comfort																
Week 12	0.7 (0.5)	NS	0.14	1.5 (0.5)	0.002	0.29	1.1 (0.7)	NS	0.21	NS		–0.25		–0.12		0.13
Week 24	0.2 (0.6)	NS	0.04	1.6 (0.5)	0.005	0.31	2.9 (0.8)	0.0003	0.55	0.026	NS	–0.41	0.008	–0.78		–0.37
IWQOL-Kids body esteem																
Week 12	2.8 (1.0)	0.004	0.27	3.4 (0.9)	0.0002	0.32	2.5 (1.2)	0.037	0.24	NS		–0.10		0.06		0.15
Week 24	2.5 (0.9)	0.009	0.24	4.1 (0.9)	<0.0001	0.39	5.6 (1.2)	<0.0001	0.54	NS		–0.30		–0.59		–0.29
IWQOL-Kids social life																
Week 12	0.5 (0.7)	NS	0.11	2.2 (0.6)	0.0008	0.44	–1.3 (0.9)	NS	–0.26	0.005	NS	–0.41	NS	0.45	0.001	0.85
Week 24	0.6 (0.6)	NS	0.12	1.4 (0.6)	0.013	0.28	1.9 (0.8)	0.019	0.37	NS		–0.23		–0.36		–0.32
IWQOL-Kids family relations																
Week 12	0.6 (0.6)	NS	0.15	1.0 (0.5)	NS	0.28	0.3 (0.7)	NS	0.08	NS		–0.14		0.08		0.22
Week 24	0.3 (0.5)	NS	0.08	0.4 (0.4)	NS	0.10	0.6 (0.6)	NS	0.15	NS		–0.03		–0.10		–0.07
IWQOL-Kids total																
Week 12	4.9 (1.9)	0.014	0.25	8.1 (1.8)	<0.0001	0.41	2.4 (2.4)	NS	0.12	NS		–0.28		0.21		0.48
Week 24	3.8 (1.9)	0.047	0.19	7.4 (1.7)	<0.0001	0.38	10.7 (2.4)	<0.0001	0.55	NS		–0.33		–0.65		–0.31

LSM – least squares mean, SE – standard error, ES – effect size, BMI – body mass index, HOMA-IR – homeostatic model of insulin resistance, HbA1c – hemoglobin A1c, HDL – high-density lipoprotein, LDL – low-density lipoprotein, CGI – Clinical Global Impression, BPRS-C – Brief Psychiatric Rating Scale for Children, IWQOL-Kids – Impact of Weight on Quality of Life-Kids

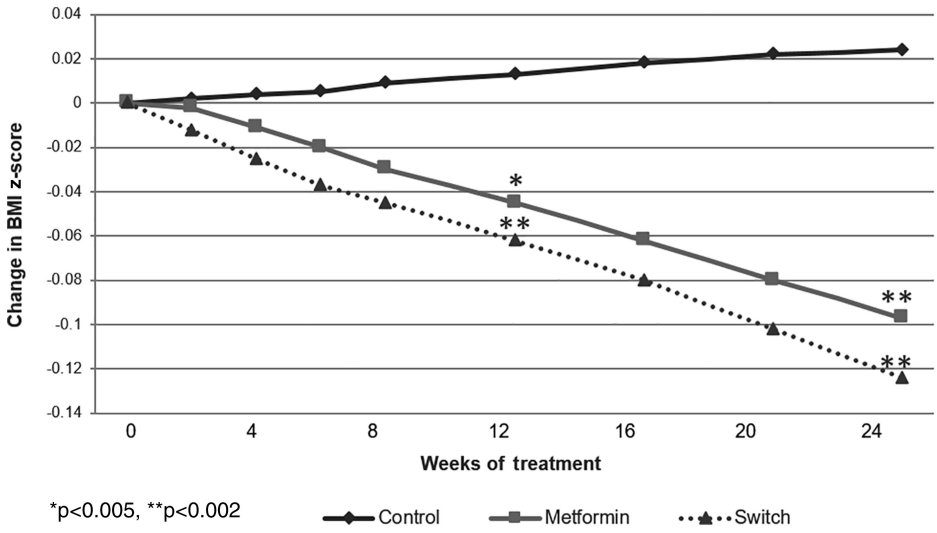

Figure 1 Estimated change in body mass index (BMI) z-score over time

10.6% of CONTROL. Furthermore, 88.6% of CONTROL subjects gained weight, with 22.7% gaining ≥7% of baseline weight, compared to only 6.1% of MET and 9.7% of SWITCH.

Metabolic parameters

Of all measured metabolic parameters, only fasting glucose at week 12 differed significantly in the 3-way comparison (p=0.001), with MET having a large effect (p=0.001, effect size 0.95) and SWITCH a medium effect (p=0.036, effect size 0.62) vs. CONTROL. MET also showed significant reductions in insulin (p=0.002) and HOMA-IR (p=0.0002) at week 12, and HgbA1c (p=0.028) at week 24. No group showed significant changes in lipids or C-reactive protein.

Psychiatric symptoms

Psychiatric symptoms, measured by the blindly-rated BPRS-C, improved in all groups and did not differ between groups (at week 24: CONTROL –4.3±1.7, MET –4.6±1.6, SWITCH –4.8±2.2). About 1/5 of each group showed much or greater improvement on the blindly-rated CGI-I. Deterioration (CGI-I ≥5) occurred in about 10% of CONTROL and MET, none of aripiprazole-SWITCH, 52.9% of perphenazine-SWITCH and the only molindone-SWITCH participant.

Weight-related quality of life improved in all groups, with the only between-treatment differences seen in the social life subscale at week 12 (p=0.005), favoring MET over SWITCH (p=0.001), and the physical comfort subscale at week 24 (p=0.026), favoring SWITCH over CONTROL (p=0.008).

Adverse events

Table 3 summarizes adverse events with overall treatment group differences of p<0.10. Discontinuations due to adverse effects were infrequent (3/47 in CONTROL, 4/46 in MET, and 1/30 in SWITCH).

Metformin was associated with significantly more abdominal pain, both moderate/severe (p=0.0074) and all severities (p=0.0066); infection, all severities (p=0.015); decreased appetite, all severities (p=0.0016); diarrhea, all severities (p=0.0016); vomiting or nausea, moderate/severe (p=0.020); and encopresis, all severities (p=0.031).

Perphenazine had numerically, but not statistically, higher proportions of both moderate/severe and all severities of hypersomnia and all severities of initial insomnia. Aripiprazole had statistically higher rates of mild dystonia (p=0.013).

MET was associated with significantly fewer problems with aggression/hostility, both moderate/severe (p=0.038) and all severities (p=0.0043), and had fewer all severity reports of anger/irritability (p=0.0049) and impulsiveness (p=0.017).

DISCUSSION

This is the first randomized trial to directly compare multiple strategies (behavioral HLE, add-on metformin, or switch to a lower weight gain-risk antipsychotic) for reducing antipsychotic-associated weight gain in youth. Weight-related outcomes for both MET and SWITCH were superior to CONTROL, with effect sizes ranging from 0.40 to 0.99, without being different from one another.

Since the weight reduction slopes in the two active arms appear to be linear, without reaching any plateau during the 6-month study period, longer studies are needed to confirm that benefits will continue to grow with time, and to determine when these benefits start to plateau.

Metabolic benefits and inflammatory changes were minimal and seemed to diminish over time. Most participants remained psychiatrically stable, except in the perphenazine-SWITCH arm, which was closed due to frequent psychiatric exacerbations resulting in discontinuation of 35.2% of subjects. Overall, both

Table 3 Adverse events with overall treatment group differences (adverse event population)

	Control (N=45)	Metformin (N=47)	Switch (N=30)	p (overall)	p (MET vs. others)
Metformin > Others (%)					
Decreased appetite, all severities	17.8	51.1	30.0	0.0028	0.0016
Diarrhea, all severities	22.2	51.1	23.3	0.0052	0.0016
Abdominal pain or discomfort, all severities	20.0	42.5	16.7	0.015	0.0066
Abdominal pain or discomfort, moderate/severe	0	10.6	0	0.026	0.0074
Infection, all severities	42.2	63.8	36.7	0.037	0.015
Vomiting or nausea, moderate/severe	0	8.5	0	0.040	0.020
Cough, all severities	17.8	34.0	13.3	0.068	0.027
Encopresis, all severities	0	10.6	3.3	0.071	0.031
Metformin < Others (%)					
Aggression or hostility, all severities	31.1	6.4	2.3	0.0085	0.0043
Aggression or hostility, moderate/severe	22.2	6.4	20.0	0.078	0.038
Anger or irritability, all severities	31.1	10.6	36.7	0.014	0.0049
Impulse control disorder, all severities	15.5	2.1	20.0	0.028	0.017
Control > Others (%)					
Abnormal weight gain, all severities	17.8	2.1	3.3	0.010	0.087
Paresthesia, all severities	6.7	0	0	0.062	NS
Restlessness, moderate/severe	6.7	0	0	0.062	NS
Switch > Others (%)					
Dystonia, all severities	0	2.1	13.3	0.019	NS
Energy increased, moderate/severe	0	0	6.7	0.059	NS
Obsessive rumination, moderate/severe	0	0	6.7	0.059	NS
Hypoacusis, all severities	4.4	0	10.0	0.067	NS

MET and aripiprazole-SWITCH were well tolerated, although MET was associated with significantly more gastrointestinal adverse effects.

Despite these adverse events, MET was not associated with significantly greater treatment discontinuation for adverse effects. This result supports the observation that most gastrointestinal adverse effects were mild to moderate, occurred early during the titration phase, and were mostly transient, or could be managed by slowing down the dose titration and/or remaining at a lower dose of metformin.

Conversely and surprisingly, MET was associated with significantly fewer reports of problems with aggression/hostility and impulsiveness than CONTROL or SWITCH. It remains unclear whether this might relate to fewer food-related struggles due to reduced appetite and/or MET's actions on glucose homeostasis in the brain or on cognition, similar to those observed in animal models[43,44].

The cardiometabolic and adverse effect results are generally consistent with those of three smaller and shorter metformin studies in antipsychotic-treated youth, demonstrating cessation of ongoing weight gain, but minimal weight loss with metformin and minimal metabolic effects over the study duration. However, this study expands upon all existing metformin studies in antipsychotic-treated individuals by also demonstrating comparable weight benefits with switch to a lower risk antipsychotic.

The minimal metabolic benefits of metformin are consistent with prior studies, and may be due to the fact that patients were selected for prior body weight gain, not metabolic abnormality. Nevertheless, individual group findings diverged somewhat from studies in adults[16-19,34,45,46], in that neither MET nor SWITCH were associated with weight loss and the HLE behavioral intervention was associated with ongoing weight gain. This difference may be related both to normal developmental mechanisms promoting ongoing growth in youth, and the prolonged antipsychotic exposure of most participants.

Additionally, relative to the physiological growth taking place during the 6-month study period, youth in the MET and SWITCH groups had negative sex- and age-adjusted BMI z-score and BMI percentile changes, whereas youth in the CONTROL group experienced not only increased body weight but also increases in BMI z-score and BMI percentile values. This result indicates that, relative to normal development, MET and SWITCH led to a reduction in body weight, whereas CONTROL was associated with weight gain in addition to what would be expected during

growth. Importantly, the differences between CONTROL and MET or SWITCH increased between week 12 (effect sizes 0.67 and 0.66) and week 24 (effect sizes 0.99 and 0.91), suggesting that continued use of MET or SWITCH likely increases the benefit.

The high rate of psychiatric destabilization with perphenazine based on blinded CGI and BPRS-C assessments was unexpected, given that this drug had comparable efficacy to multiple SGAs in adults with schizophrenia[33]. However, its efficacy for pediatric psychotic and mood disorders has never been evaluated. The observed destabilization does not appear to be the result of too rapid a switch (given the very slow plateau cross-titration and the fact that 41.2% failed to discontinue their baseline antipsychotic) or extrapyramidal adverse effects (given the use of prophylactic anticholinergic treatment and only mild parkinsonian symptoms in two participants). However, adverse events limited our ability to increase the perphenazine dose as much as desired, suggesting a reduced benefit-risk ratio of perphenazine in youth.

The results of this study need to be interpreted within its limitations. First, although this was the largest metformin study conducted to date in antipsychotic-treated youth, individual group sizes were still modest, especially in the SWITCH arm, and secondary analyses were not corrected for multiple testing. Metabolic changes might be more evident in a larger sample.

Second, there was a smaller number of participants in the SWITCH arm. Reasons included the halted randomization from when molindone was discontinued in the US market until approval of the perphenazine-SWITCH arm, and later stoppage of switch to perphenazine due to increased psychiatric worsening. Since perphenazine-SWITCH was not well tolerated and led to substantial discontinuation due to inefficacy, additional agents with low weight gain potential need to be studied. In this context, it remains unclear if switching from one lower risk agent, like aripiprazole, to another "lower risk" agent, including ziprasidone and lurasidone, or (based on adult data) cariprazine or brexpiprazole, would have similar effects to SWITCH in this study[5,47,48].

Third, we did not compare MET or SWITCH to a formal weight loss intervention, but rather used HLE, consisting of education and close weight monitoring. Future studies are needed to investigate the efficacy of a formal weight loss intervention in overweight/obese, antipsychotic-treated youth. Although prior studies suggested that formal weight loss interventions were efficacious in adults with antipsychotic-induced weight gain[18], the largest study of a behavioral weight loss intervention in antipsychotic-treated adults failed to demonstrate its superiority to treatment-as-usual[22].

Fourth, this was an open study without placebo control, likely influencing some participants to withdraw immediately post-randomization. However, open treatment increased the ecologic validity of our findings, the majority of outcomes were objective measurements, and the BPRS-C and CGI were assessed by blinded evaluators, minimizing risk of bias.

Fifth, we decided on a relatively slow metformin titration over 4 weeks, in order to minimize dose- and titration-dependent adverse effects that could have increased undesirable drop-out rates. While it is possible that a faster metformin titration could have yielded larger effects, the rather linear slope of the BMI z-score change does not suggest major acceleration of the efficacy as higher doses were achieved.

Sixth, patients could be on a total of three (or four, if two medications were used for ADHD) psychotropic medications. While co-medication effects could potentially have confounded the results, this study methodology assured higher generalizability, as patients receiving antipsychotics often are on multiple psychotropic drugs. Further, the randomized groups differed by only 3-5% regarding use of psychostimulants and antidepressants and 8-14% concerning use of mood stabilizers.

Finally, while the rate of concomitant psychostimulant treatment was relatively high across the three intervention groups (40-45%), this unlikely affected the results. Prior studies have shown that antipsychotic-related weight gain is not moderated or diminished by concomitant psychostimulant use[49,50]. Moreover, patients in this study all had significant weight gain despite the fact that they received concomitant psychostimulant treatment that was kept stable during the study.

In summary, our results provide evidence that both MET and switch to aripiprazole reduce SGA-related weight gain burden in youth. Further study is required to determine whether, as suggested in adults[21], the benefits of MET might be stronger in youth with more limited weight gain or during antipsychotic initiation[51]. However, the minimal effect observed on metabolic outcomes mandates routine metabolic monitoring and careful consideration of other treatment strategies with lower risk for weight gain prior to the antipsychotic initiation[52].

Further, although aripiprazole switch was associated with significant reductions in weight measures vs. the control group, the high prevalence of its current (46.4%) and prior (26.0%) use in this sample suggests that a limited subset of children may benefit from this strategy. Evaluation of other potential switch agents, metformin's prophylactic use, other agents that may mitigate antipsychotic-associated weight gain, and the potential benefit of MET for aggression is warranted in youth.

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The interplay among psychopathology, personal resources, context-related factors and real-life functioning in schizophrenia: stability in relationships after 4 years and differences in network structure between recovered and non-recovered patients

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Improving real-life functioning is the main goal of the most advanced integrated treatment programs in people with schizophrenia. The Italian Network for Research on Psychoses previously explored, by using network analysis, the interplay among illness-related variables, personal resources, context-related factors and real-life functioning in a large sample of patients with schizophrenia. The same research network has now completed a 4-year follow-up of the original sample. In the present study, we used network analysis to test whether the pattern of relationships among all variables investigated at baseline was similar at follow-up. In addition, we compared the network structure of patients who were classified as recovered at follow-up versus those who did not recover. Six hundred eighteen subjects recruited at baseline could be assessed in the follow-up study. The network structure did not change significantly from baseline to follow-up, and the overall strength of the connections among variables increased slightly, but not significantly. Functional capacity and everyday life skills had a high betweenness and closeness in the network at follow-up, as they had at baseline, while psychopathological variables remained more peripheral. The network structure and connectivity of non-recovered patients were similar to those observed in the whole sample, but very different from those in recovered subjects, in which we found few connections only. These data strongly suggest that tightly coupled symptoms/dysfunctions tend to maintain each other's activation, contributing to poor outcome in schizophrenia. Early and integrated treatment plans, targeting variables with high centrality, might prevent the emergence of self-reinforcing networks of symptoms and dysfunctions in people with schizophrenia.

Key words: Schizophrenia, network analysis, real-life functioning, psychopathology, personal resources, internalized stigma, recovery, functional capacity, everyday life skills

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Improving real-life functioning is the main goal of the most advanced integrated treatment programs in people with schizophrenia[1-4]. Research has clarified that real-life functioning in these people does not depend exclusively on psychopathology, but is influenced by a range of variables, some of which are illness-related, while others are relevant to the personal resources of the individual, or are context-related[5-8].

In order to advance knowledge on the relative impact of the above variables on real-life functioning in people with schizophrenia, the Italian Network for Research on Psychoses carried out a large multicenter study involving 921 community-dwelling, clinically stable patients with that diagnosis[9,10]. That study (from here on referred to as the baseline study) assessed a larger number of variables as compared with all previous relevant investigations, some of them never explored before.

The interplay of 27 variables concerning the illness, personal resources, social context and real-life functioning was investigated using network analysis. This analytical approach makes it possible to interpret the correlations among a large number of variables by providing a clear-cut picture of the relevant links. Moreover, it provides useful insights about the most central variables in the network, which may inform clinicians about possible therapeutic targets.

In our baseline study, functional capacity and everyday life skills were the most central and interconnected nodes of the network, while psychopathological variables were more peripheral[10]. Social cognition, neurocognition, resilience, and the three domains of real-life functioning of interest for community dwell-

ing people with schizophrenia (work skills, interpersonal relationships and everyday life skills) formed highly interconnected, spatially contiguous clusters.

The Italian Network for Research on Psychoses has now completed a 4-year follow-up of the original sample. In the present study, we tested whether the pattern of relationships among illness-related variables, personal resources, context-related factors and real-life functioning was similar at follow-up versus baseline in patients assessed at both waves.

In addition, we aimed to compare the network structure of patients who achieved recovery at follow-up versus those who did not recover. Based on the few previous reports on changes in network structures in remitted versus non-remitted subjects with various diagnoses, covering psychopathological but not functional variables[11-13], we expected a less interconnected network structure in recovered than in non-recovered subjects.

METHODS

Participants

All 921 patients recruited for the baseline study by the 26 Italian university psychiatric clinics and/or mental health departments participating in the baseline study[9] were asked to join the follow-up study. Subjects were contacted by phone, e-mail or during a routine follow-up visit or rehabilitation session.

The inclusion criterion was a diagnosis of schizophrenia according to DSM-IV, confirmed by the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P)[14]. Exclusion criteria were: a history of head trauma with loss of consciousness in the 4-year interval between baseline and follow-up; progressive cognitive deterioration possibly due to dementia or other neurological illness diagnosed in the last 4 years; a history of alcohol and/or substance abuse in the last 6 months; current pregnancy or lactation; inability to provide an informed consent; treatment modifications and/or hospitalization due to symptom exacerbation in the last 3 months.

When participants in the baseline study could not be traced or were deceased, investigators were asked to fill in an *ad hoc* form reporting clinical information available at the last contact and, in the relevant cases, the cause of death.

All patients were asked to sign a written informed consent to participate, after receiving a comprehensive explanation of the study procedures and goals. Approval of the study protocol was obtained from the Local Ethics Committees of the participating centers. Recruitment took place from March 2016 to December 2017.

Procedures

Enrolled patients completed the assessments in three days, with the following schedule: on day 1, in the morning, collection of socio-demographic information, psychopathological evaluation and neurological assessment; on day 2, in the morning, assessment of neurocognitive functions, social cognition and functional capacity; on day 3 (morning or afternoon) or in the afternoon of day 1 or 2, according to the patient's preference, assessment of personal resources and perceived stigma. For real-life functioning assessment, patient's key caregiver was invited to join one of the scheduled sessions.

Assessment tools

Illness-related factors

With the support of all available sources of information (patients, relatives, medical records and mental health workers), a clinical form was filled in with data on disease course and treatments in the previous 4 years.

The Positive and Negative Syndrome Scale (PANSS)[15] was used to assess symptom severity. In line with the baseline study[10], the scores for the dimension "positive symptoms" were calculated based on the consensus 5-factor solution proposed by Wallwork et al[16]. "Disorganization" was the PANSS item P2, to avoid overlap with cognitive impairment. Negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS)[17], which includes five negative symptom domains: anhedonia, asociality, avolition, blunted affect and alogia; for the purpose of the present paper, as already done in our previous network analysis[10], we used two factors: "expressive deficit" (sum of the subscales blunted affect and alogia) and "avolition" (sum of the subscales anhedonia, asociality and avolition).

Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS)[18]. Extrapyramidal symptoms were assessed by means of the St. Hans Rating Scale (SHRS)[19], a multidimensional rating scale consisting of four subscales: hyperkinesia, parkinsonism, akathisia and dystonia.

Neurocognitive functions were rated using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[20,21]. This battery includes tests for the assessment of seven cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, social cognition, and reasoning and problem solving.

The assessment of social cognition, partly included in the managing emotion section of the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), was integrated by the Facial Emotion Identification Test (FEIT)[22] and The Awareness of Social Inference Test (TASIT)[23], which includes three sections (TASIT 1-3), exploring emotion recognition (TASIT 1) and theory of mind (TASIT 2 and 3).

Personal resources

Resilience was evaluated by the Resilience Scale for Adults (RSA)[24], a self-administered scale including 33 items that examine intra- and inter-personal protective factors thought to facili-

tate adaptation when facing psychosocial adversity. As described in Galderisi et al[9], to avoid overlap with other measures, only the factors "perception of self", "perception of the future", "social competence" and "family cohesion" were included in the analysis.

The Service Engagement Scale (SES)[25], an instrument including 14 items, rated on a 4-point Likert scale (with higher scores reflecting greater levels of difficulty engaging with services), was used to assess patient's availability, cooperation, help-seeking and treatment attitude. In the present paper, we used the total score.

Context-related factors

The availability of a disability pension, access to family practical and financial support, and registration in the unemployment list were recorded as a count variable, ranging from 0 to 4.

The Internalized Stigma of Mental Illness (ISMI)[26] was used to evaluate the experience of stigma and internalized self-rejection.

Functional capacity and real-life functioning

The short version of the University of California San Diego (UCSD) Performance-based Skills Assessment Brief (UPSA-B)[27], a performance-based instrument that assesses "financial skills" (e.g., counting money and paying bills) and "communication skills" (e.g., to dial a telephone number for emergency or reschedule an appointment by telephone) was used to assess functional capacity.

Real-life functioning was assessed by the Specific Level of Functioning Scale (SLOF)[28], a hybrid instrument that explores many aspects of functioning and is based on the key caregiver's judgment on patient's behavior and functioning. SLOF "interpersonal relationships", "everyday life skills" and "work skills" domains were included in statistical analyses. The SLOF was administered to the key caregiver, i.e. the person most frequently and closely in contact with the patient.

Training of researchers

A centralized training of researchers was conducted two months before starting the follow-up recruitment, to ensure comparability of data collection procedures.

For each category of variables (illness-related factors, personal resources and context-related factors), at least one researcher per site was trained. In order to avoid halo effects, the same researcher could not be trained for more than one category.

The inter-rater reliability was formally evaluated by Cohen's kappa for categorical variables, and intraclass correlation coefficient (ICC) for continuous variables. For items showing a small degree of variation among patients (whose ICC would not be meaningful, since it is based on a ratio of between- and within-patient variation), the percentage of perfect agreement was calculated as an alternative expression of inter-rater reliability.

An excellent inter-rater agreement was found for the SCID-I-P (Cohen's kappa=0.91). Good to excellent agreement among raters was observed for SLOF (ICC=0.58-1.00, percentage agreement = 70-100%), BNSS (ICC=0.74-0.97), PANSS (ICC=0.60-0.98, percentage agreement = 64-100%), CDSS (ICC=0.76-0.98) and MCCB (ICC=0.98).

Statistical analyses

Patients who participated in the 4-year follow-up were compared with those who did not participate on gender, age, education, and on the 27 baseline variables related to illness, personal resources, context and real-life functioning, to determine whether they were representative of the original sample[9]. Between-group comparisons were performed using the X^2 test, the t-test or Mann-Whitney test, depending on the type of measurement and the distribution of variables. Bonferroni-Holm correction was applied to comparisons of scale scores to control for type-I error inflation.

To ensure pairwise comparability of baseline and follow-up data of patients assessed at each time point, missing data were imputed using an expectation-maximization algorithm, assuming that the pattern of missing data was random. This assumption allows estimates to be adjusted using available information. Overall, 201 values (1.1%) were imputed at baseline and 756 values (4.1%) at follow-up. Within-subject comparisons at baseline and follow-up were conducted using the paired-sample t-test, Wilcoxon test or McNemar's test.

Patients were classified as recovered or non-recovered at the 4-year follow-up according to two criteria: one based on the presence or absence of symptomatic remission according to Andreasen et al (severity criterion)[29], and the other based on the presence or absence of functional recovery, defined as a weighted score of at least 76.2 on SLOF "interpersonal relationships", "work skills" and "everyday life skills" scales. This latter cut-off was identified through a preliminary receiver operating characteristic (ROC) analysis on Galderisi et al's sample[9] using a Personal and Social Performance (PSP) score ≥71 as the gold standard[30]. That cut-off identified patients with vs. without functional recovery with a sensitivity of 86.9%, a specificity of 68.5%, and an area under the curve of 0.84.

We then compared the pattern of relationships among study variables at baseline and follow-up in the overall study population, and between recovered and non-recovered patients at follow-up, using network analysis.

A network is a graphical representation that includes nodes (variables) and edges (correlations among variables). The network structure of the 27 study variables at baseline and follow-up was estimated using the statistical package JASP, version 0.10.2 (https://jasp-stats.org/). A non-paranormal transformation was performed prior to the analysis to relax the normality assumption, because variables were not normally distributed[31]. The least absolute shrinkage and selection operator (LASSO)[32] was used

Table 1 Socio-demographic and clinical variables at follow-up (N=618)

Gender (% males)	69.1
Age (years, mean±SD)	45.1±10.5
Married (%)	7.4
Working (%)	34.4
Education (years, mean±SD)	11.7±3.4
Stable affective relationships (%)	18.9
Current drug treatment	
First-generation antipsychotics (%)	13.1
Second-generation antipsychotics (%)	69.3
Both first- and second-generation antipsychotics (%)	15.0
Antidepressants (%)	17.6
Mood stabilizers (%)	26.0
Anxiolytics (%)	32.7
Anticholinergics (%)	9.4
Polypharmacy (%)	54.4
Any psychosocial interventions (%)	34.3
Psychoeducation (%)	3.4
Cognitive training (%)	7.9
Social skills training (%)	3.6
Vocational training (%)	4.2
Leisure time activities (%)	17.6
Art therapy (%)	5.8
Self-management (%)	0.5
Other (%)	3.1
Psychotherapy (%)	14.9
Home care (%)	8.3
Currently in a residential facility (%)	10.1
Relapse during past 4 years (%)	43.5
Substance abuse (%)	5.0
Alcohol abuse (%)	4.9
Smoking (%)	42.1
Unhealthy eating habits (%)	25.9

to reduce the number of false-positive edges and to improve the interpretability of the network. This procedure applies a penalty to small edges by setting them to zero. The shrinkage parameter that optimized the number of edges was selected by minimizing the extended Bayesian information criterion (EBIC) parameter[33].

The location of nodes was based on the Fruchterman-Reingold algorithm[34], that places nodes with stronger or more connections close to each other and nodes with weaker connections at the periphery of the network. We constrained the layout of the networks to be the same at baseline and follow-up to facilitate visual comparison of the edges at the two time points. Three centrality indices of the network were calculated for all variables at baseline and follow-up. Strength or degree centrality is the sum of the absolute values of the edges of a given node to other nodes. The two other centrality measures are betweenness, i.e. the number of times a node lies on the shortest path length between any two other nodes, and closeness, that indicates how easy it is to reach all other nodes from the node of interest. Centrality measures were standardized to facilitate comparisons.

The robustness of the network solution was assessed by estimating the accuracy of edge weights and the stability of centrality indices using non-parametric bootstrapping procedures

Table 2 Network variables at baseline and follow-up (N=618)

	Baseline (mean±SD)	Follow-up (mean±SD)
PANSS positive	9.7±4.7	8.4±4.3*
PANSS disorganization	2.6±1.4	2.4±1.4*
BNSS avolition	20.7±9.6	18.6±9.7*
BNSS expressive deficit	12.7±7.9	12.0±7.7*
CDSS total score	3.9±4.0	3.2±3.7*
RSA - Perception of self	18.1±5.3	15.4±4.6*
RSA - Perception of the future	10.7±4.2	10.8±4.2
RSA - Social competence	19.0±5.3	19.0±5.3
RSA - Family cohesion	20.4±5.7	20.5±5.3
MCCB - Reasoning and problem solving	9.8±6.5	9.6±6.6
MCCB - Attention/vigilance	1.7±0.8	1.6±0.9
MCCB - Visual learning	16.3±8.7	16.0±8.1
MCCB - Verbal learning	19.1±5.4	19.5±5.5*
MCCB - Processing speed	94.6±18.3	95.5±21.0
MCCB - Working memory	11.4±3.7	11.2±3.8*
TASIT 1	20.1±4.9	20.4±4.8*
TASIT 2	37.6±10.9	38.6±10.2*
TASIT 3	38.4±11.0	38.7±9.7
Facial Emotion Identification Test	37.0±8.3	37.3±8.1
MSCEIT	79.0±9.0	90.6±14.1*
UPSA-B total score	67.3±21.6	68.6±23.9
SLOF everyday life skills	46.2±8.3	45.2±9.5*
SLOF interpersonal relationships	22.8±5.9	21.2±6.0*
SLOF work skills	20.4±6.0	20.1±6.1
Service Engagement Scale	12.2±7.5	11.5±8.0
ISMI (without Stigma resistance)	2.2±0.4	2.1±0.5*
Number of incentives	1.8±1.1	1.9±1.1**

PANSS – Positive and Negative Syndrome Scale, BNSS – Brief Negative Symptom Scale, CDSS – Calgary Depression Scale for Schizophrenia, RSA – Resilience Scale for Adults, MCCB – Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery, TASIT – The Awareness of Social Inference Test, MSCEIT – MCCB Mayer-Salovey-Caruso Emotional Intelligence Test, UPSA-B – UCSD Performance-Based Skills Assessment, SLOF – Specific Level of Functioning Scale, ISMI – Internalized Stigma of Mental Illness
*significant t-test after Bonferroni-Holm correction, **significant Mann-Whitney test after Bonferroni-Holm correction

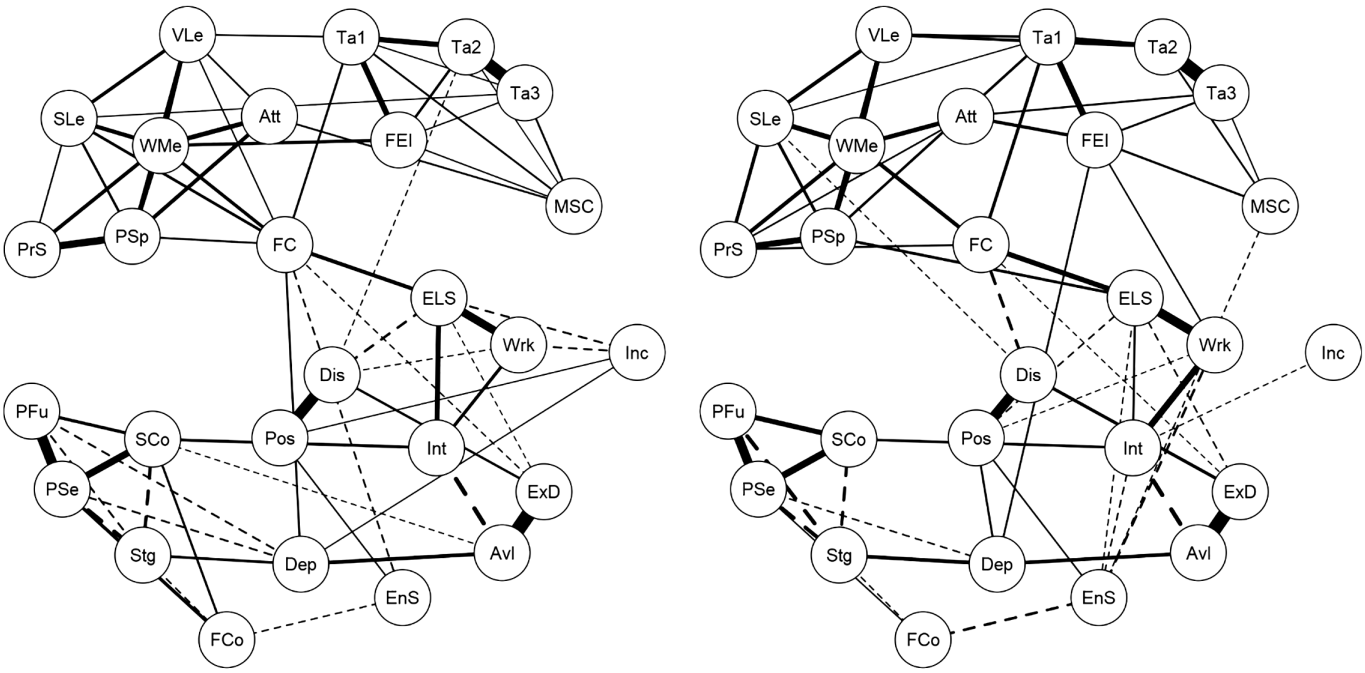

Figure 1 Network showing the associations among study variables at baseline (left) and follow-up (right). Broken edges indicate inverse associations, full edges direct correlations. The thickness of an edge reflects the magnitude of the correlation. Att – attention, Avl – avolition, Dep – depression, Dis – disorganization, ELS – everyday life skills, EnS – service engagement, ExD – expressive deficit, FC – functional capacity, FCo – family cohesion, FEI – Facial Emotion Identification Test, Inc – number of incentives, Int – interpersonal relationships, MSC – Mayer-Salovey-Caruso Emotional Intelligence Test, PFu – perception of the future, Pos – positive symptoms, PrS – problem solving, PSe – perception of self, PSp – processing speed, SCo – social competence, SLe – visuospatial learning, Stg – stigma, Ta – The Awareness of Social Inference Test (TASIT), VLe – verbal learning, WMe – working memory, Wrk – work skills

described by Epskamp et al[35]. Specifically, the accuracy of edge weights was measured by the 95% confidence intervals (CIs) obtained from 1,000 bootstrap samples drawn from the study population: the narrower the CI, the more accurate is the estimate of the edge weights. We also evaluated the stability of the centrality indices by using the node-dropping subset bootstrap[35]. To this purpose, we randomly sampled a network of 26 nodes 1,000 times and repeated the procedure for networks between 25 and 2 nodes. We then estimated the mean node strength of each variable for all subset networks, to determine the extent to which the network was robust to the exclusion of some nodes.

To further examine the robustness of our findings, we compared the standard deviations (SDs) of each variable included in the networks between the two time points by means of Levene's test. If SDs change significantly, differences in the network structure might be a result of increased variation over time.

Differences in network structure and global strength between and within subjects were tested for significance using the M-test and the S-test included in the R-package network comparison test (NCT), which uses permutation testing to compare networks[36]. The paired-sample option was used to compare the same group at baseline and follow-up, and independent-sample comparisons were used when two groups were compared at the same time point.

RESULTS

Characteristics of participants

Twenty-four out of the 26 Italian university psychiatric clinics and/or mental health departments who had contributed to the baseline study participated in the follow-up. The two remaining centers could not join the follow-up study due to changes in their organization. Six hundred eighteen subjects out of the 921 recruited at baseline were included in the follow-up study.

Twenty-four patients had been recruited at the two sites that did not participate in the follow-up study; 19 had deceased; 10 could not be traced; 98 refused to participate; 75 were now being followed by a different psychiatrist or mental health department; 36 had changed residence and reported logistic difficulties to join the study; 24 were clinically unstable and/or had recently changed pharmacological treatment; 4 showed a significant cognitive decline, possibly due to dementia; 2 reported substance abuse in the past 6 months. In the remaining 11 individuals, reasons for not participating were not specified.

Patients who participated in the 4-year follow-up did not differ significantly from the rest of the sample (N=303) on baseline socio-demographic characteristics, illness-related variables and context-related factors. However, follow-up participants had sig-

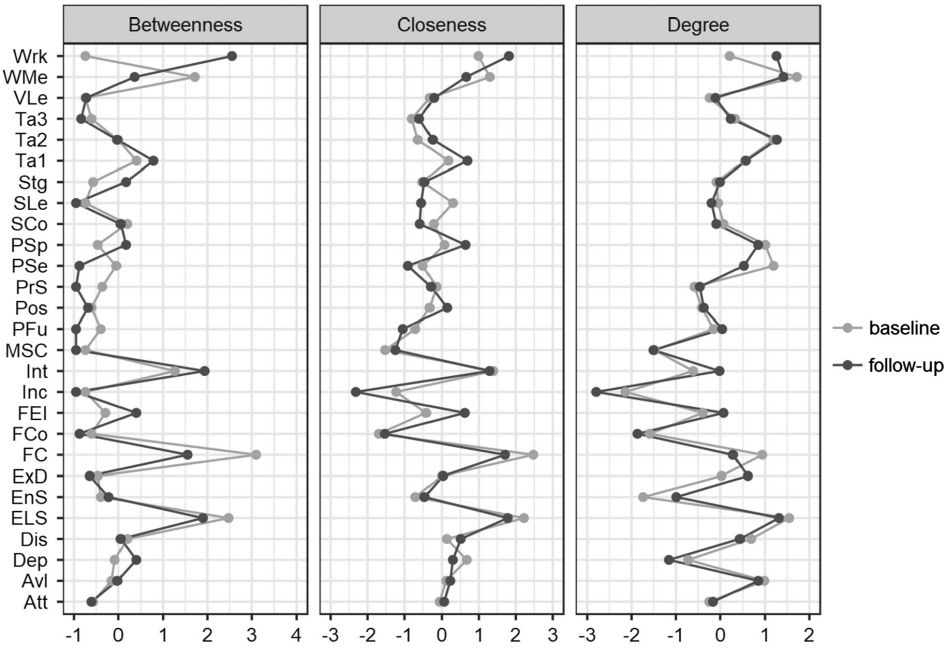

Figure 2 Centrality measures of the study variables at baseline and follow-up. Att – attention, Avl – avolition, Dep – depression, Dis – disorganization, ELS – everyday life skills, EnS – service engagement, ExD – expressive deficit, FC – functional capacity, FCo – family cohesion, FEI – Facial Emotion Identification Test, Inc – number of incentives, Int – interpersonal relationships, MSC – Mayer-Salovey-Caruso Emotional Intelligence Test, PFu – perception of the future, Pos – positive symptoms, PrS – problem solving, PSe – perception of self, PSp – processing speed, SCo – social competence, SLe – visuospatial learning, Stg – stigma, Ta – The Awareness of Social Inference Test (TASIT), VLe – verbal learning, WMe – working memory, Wrk – work skills

nificantly higher scores (i.e., better functioning) on two SLOF scales ("interpersonal relationships": 22.8±5.9 vs. 21.3±6.3, t=3.51, p<0.001; "work skills": 20.4±6.0 vs. 19.2±6.5, t=2.68, p=0.008) and a higher engagement with mental health services (12.2±7.5 vs. 14.4±7.9, t=–3.98, p<0.001). These mean differences in scale scores were relatively small and not clinically relevant; thus, the 618 patients participating in the follow-up study can be considered representative of the original sample.

Socio-demographic and clinical characteristics of the 618 patients at follow-up are reported in Table 1. They were predominantly males (69.1%), with a mean age of 45.1 years and an average of 11.7 years of education. A moderate increase from baseline was found in the percentage of subjects with a job (from 29.2% to 34.4%; McNemar's test = 11.4, p=0.001) and with a stable affective relationship (from 14.9% to 18.9%, McNemar's test = 7.7, p=0.006).

Almost all subjects were on antipsychotic treatment (97.4%; 13.1% on first-generation antipsychotics; 69.3% on second-generation antipsychotics; 15.0% on both; 2.1% on no antipsychotic; for 0.5% no information was available). Polypharmacy was reported by 54.4% of patients. At least one psychosocial intervention was received by 34.3% of participants; 9.1% received two interventions, 4.1% three or more.

At least one relapse was reported in 43.5% of the sample during the previous 4 years; among patients who relapsed, the median number of relapses was 2.

Descriptive statistics of variables included in the network analysis

The mean values and SDs of all variables included in the network analysis at baseline and follow-up are reported in Table 2.

In the overall sample of 618 subjects participating in the follow-up study, we found improvements in severity of positive symptoms, disorganization, avolition, expressive deficit, depression and internalized stigma. Most social cognition variables improved, while neurocognition variables were quite stable, with significant changes only for verbal learning (slightly improved) and working memory (slightly worsened). Resilience variables were also stable, and only perception of self slightly worsened at follow-up. Everyday life skills and interpersonal relationships also slightly deteriorated. Although significant, these mean differences in scale scores were relatively small and not clinically relevant.

Network analysis of the whole sample

Figure 1 shows the baseline and follow-up networks of the overall sample. The network structure did not change significantly from baseline to follow-up (M-test = 0.13, p=0.154), suggesting that links among variables were stable over time. The overall strength of the connections among variables increased slightly, but not significantly (11.18 vs. 11.75, S-test = 0.57, p=0.196).

Table 3 Socio-demographic and clinical variables in non-recovered and recovered patients

	Non-recovered (N=494)	Recovered (N=124)	p
Gender (% males)	70.0	65.3	0.309
Age (years, mean±SD)	45.9±10.4	41.8±10.1	<0.001
Married (%)	6.9	9.7	0.289
Working (%)	26.2	67.2	<0.001
Education (years, mean±SD)	11.5±3.3	12.7±3.4	<0.001
Stable affective relationships (%)	15.1	34.4	<0.001
Current drug treatment			
First-generation antipsychotics (%)	14.2	8.9	0.118
Second-generation antipsychotics (%)	66.8	79	0.008
Both first- and second-generation antipsychotics (%)	17.0	7.3	0.007
Antidepressants (%)	17.6	17.5	0.975
Mood stabilizers (%)	26.6	23.3	0.459
Anxiolytics (%)	36.7	16.7	<0.001
Anticholinergics (%)	11.3	1.7	<0.001
Polypharmacy (%)	57.6	41.7	0.002
Any psychosocial intervention (%)	39.7	40.3	0.895
Psychoeducation (%)	3.8	1.6	0.22
Cognitive training	6.9	12.1	0.055
Social skills training (%)	3.6	3.2	0.822
Vocational training (%)	3.0	8.9	0.004
Leisure time activities (%)	19.0	12.1	0.07
Art therapy (%)	5.3	8.1	0.234
Self-management (%)	0.6	0	0.384
Other (%)	3.6	0.8	0.102
Psychotherapy (%)	9.7	14.5	0.122
Home care (%)	9.3	4.0	0.056
Currently in a residential facility (%)	11.5	4.8	0.029
Relapse during past 4 years (%)	45.5	36.6	0.074
Substance abuse (%)	4.0	8.9	0.028
Alcohol abuse (%)	5.5	2.4	0.157
Smoking (%)	43.1	38.1	0.331
Unhealthy eating habits (%)	26.2	24.2	0.621

Visual inspection revealed broad similarities between the two networks, i.e. nodes belonging to the same construct were spatially contiguous and highly interconnected. Moreover, psychopathology variables were less interconnected than those belonging to other constructs, such as neurocognition, social cognition and resilience, consistent with the findings reported by Galderisi et al[10].

Some new connections emerged at follow-up, in particular: service engagement with SLOF scales (work skills, everyday life skills, and interpersonal relationships) and MSCEIT; attention with TASIT 1 and 3; incentives with interpersonal skills; depression with positive symptoms and FEIT; disorganization with functional capacity and spatial learning; FEIT with work skills; and processing speed with everyday life skills.

Few connections were no longer present at follow-up, in particular: incentives with depression, positive symptoms, everyday life activities and work skills; service engagement with functional capacity; and avolition with social competence.

Notably, at both baseline and follow-up, functional capacity and everyday life skills had high centrality, especially because they were in the pathways connecting functioning, social cognition, neurocognition and psychopathology. At both time points,

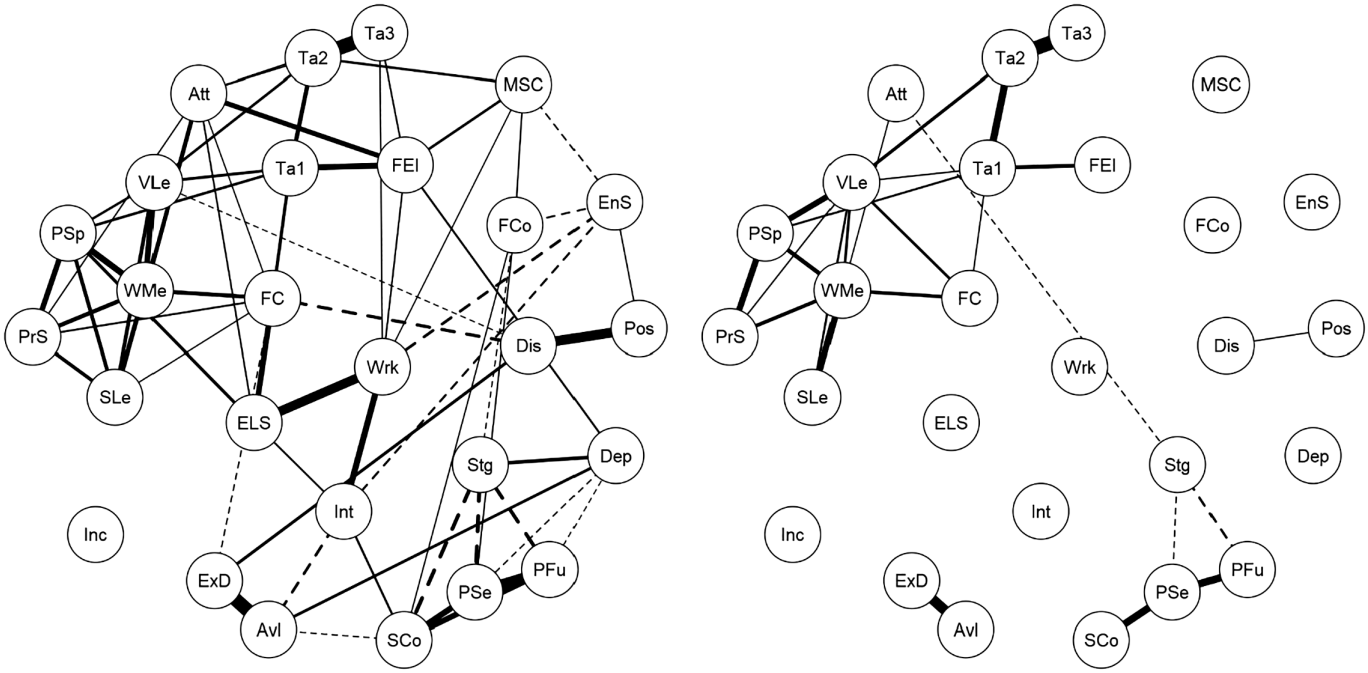

Figure 3 Network showing the associations among study variables among non-recovered (left) and recovered (right) patients. Broken edges indicate inverse associations, full edges direct correlations. The thickness of an edge reflects the magnitude of the correlation. Att – attention, Avl – avolition, Dep – depression, Dis – disorganization, ELS – everyday life skills, EnS – service engagement, ExD – expressive deficit, FC – functional capacity, FCo – family cohesion, FEI – Facial Emotion Identification Test, Inc – number of incentives, Int – interpersonal relationships, MSC – Mayer-Salovey-Caruso Emotional Intelligence Test, PFu – perception of the future, Pos – positive symptoms, PrS – problem solving, PSe – perception of self, PSp – processing speed, SCo – social competence, SLe – visuospatial learning, Stg – stigma, Ta – The Awareness of Social Inference Test (TASIT), VLe – verbal learning, WMe – working memory, Wrk – work skills

working memory had the highest strength, because of its strong correlations with the other neurocognition variables. All centrality measures were similar across the two time points, except for work skills, that had a higher centrality at follow-up, especially for betweenness (Figure 2).

The edge weight estimations were accurate at each time point, since the bootstrap mean of each edge and the original value were almost overlapping and the CIs of edge weights estimates were all narrow. As to the robustness of centrality indices, results indicate that the correlation between the strength centrality calculated on the "reduced" networks and that on the original network was >0.70 until 30% of nodes (i.e., at least 9 out of 27) were sampled. This indicates that the relationships between variables remained stable even after random elimination of some network nodes.

Characteristics of recovered and non-recovered patients

At the 4-year follow-up, 124 patients met criteria for recovery (20.1%) and 494 (79.9%) were non-recovered. Table 3 shows that, compared with patients who did not recover, those who recovered were significantly younger, more educated, more likely to be working and to have a stable affective relationship. Moreover, substance abuse was more common among recovered patients, and they were less likely to live in a residential facility.

Concerning treatments, the proportion of patients receiving any psychosocial intervention was similar in the two groups. However, patients who recovered were receiving vocational training more frequently. Pharmacological treatment with antipsychotics was provided to almost all patients. Treatment with second-generation antipsychotics was more common in recovered individuals, while treatment with both first- and second-generation antipsychotics was more common in non-recovered individuals. Polypharmacy, i.e. prescription of drugs of two different classes, was more common among non-recovered patients, who more often received treatment with anxiolytics and anticholinergic drugs.

Network analysis of recovered and non-recovered patients

Figure 3 shows the follow-up network structure of patients who recovered and those who did not recover. The network structure and connectivity of non-recovered patients were similar to those observed in the whole sample, but very different from those found in recovered subjects. Actually, in these latter individuals, only few connections were found: positive symp-

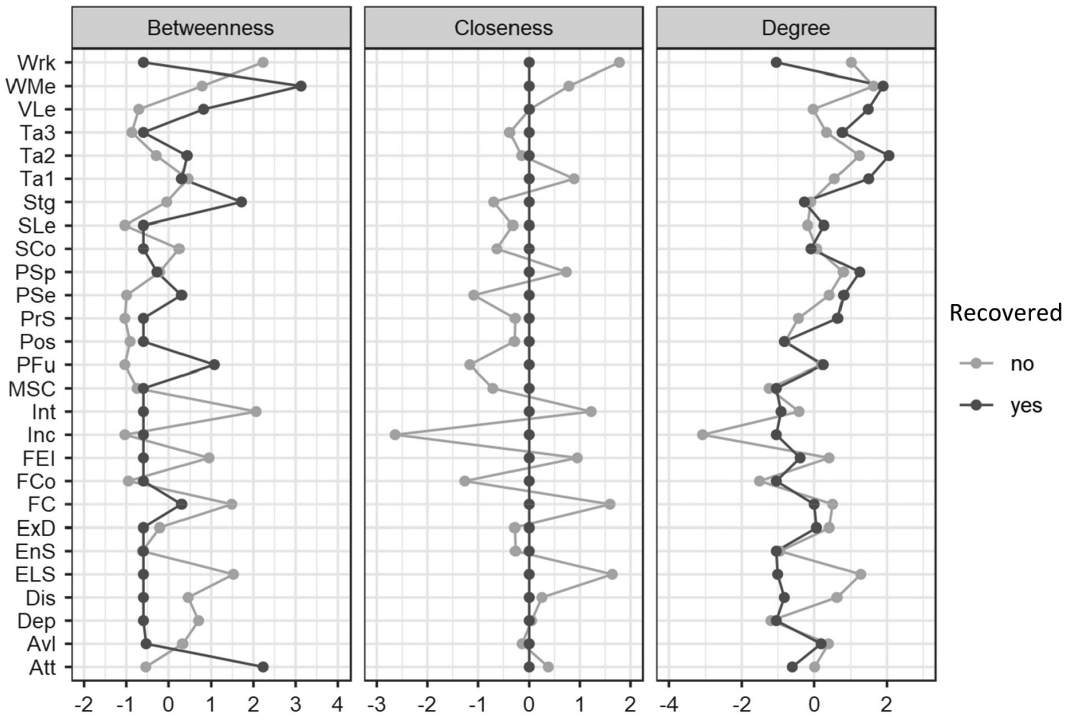

Figure 4 Centrality measures among non-recovered and recovered patients. Because some nodes are disconnected among recovered patients, closeness is always 0 by definition in this group. Att – attention, Avl – avolition, Dep – depression, Dis – disorganization, ELS – everyday life skills, EnS – service engagement, ExD – expressive deficit, FC – functional capacity, FCo – family cohesion, FEI – Facial Emotion Identification Test, Inc – number of incentives, Int – interpersonal relationships, MSC – Mayer-Salovey-Caruso Emotional Intelligence Test, PFu – perception of the future, Pos – positive symptoms, PrS – problem solving, PSe – perception of self, PSp – processing speed, SCo – social competence, SLe – visuospatial learning, Stg – stigma, Ta – The Awareness of Social Inference Test (TASIT), VLe – verbal learning, WMe – working memory, Wrk – work skills

toms and disorganization were connected to each other, as well as avolition and expressive deficit; neurocognitive (with working memory showing the highest betweenness), resilience and social cognition variables remained interconnected within and between domains. Instead, the three domains of real-life functioning were not interrelated and were disconnected from the other domains. Incentives, engagement with services, depression, family cohesion and MSCEIT were isolated from the rest of the network.

The strength of connections was significantly higher in non-recovered than in recovered patients (S-test = 9.156, $p<0.001$) and the network structure was remarkably different between the two subgroups (M-test = 0.371, $p=0.002$). Concerning centrality measures, only strength (degree) could be compared between the two groups, because it is the sum of edges connecting each node to the others, while closeness was always zero among non-recovered individuals, as some nodes were disconnected, and betweenness was irrelevant given the sparsity of the network (Figure 4). We found that everyday life skills and disorganization had a higher strength among non-recovered patients.

Bootstrap tests indicated that edges were accurate in non-recovered and less so among recovered patients, in which larger 95% CIs were obtained. The strength centrality remained stable in both patient groups until 40% (i.e., at least 11 out of 27) of nodes were sampled.

DISCUSSION

Our follow-up study aimed at two main goals: a) to assess the long-term stability in the pattern of relationships among illness-related variables, personal resources, context-related factors and real-life functioning in subjects with schizophrenia recruited for the multicenter investigation of the Italian Network for Research on Psychoses; b) to compare the network structure of patients who were classified as recovered versus those who were non-recovered.

Subjects participating at both time points were living in the community and stabilized on antipsychotic treatment. We could detect some significant changes from the baseline. In particular, more subjects had a job and stable affective relationships. However, on average, real-life functioning had slightly worsened, in spite of small, not clinically significant improvements in psychopathology and social cognition.

The baseline and follow-up networks did not show significant differences. At both time points, variables relevant to the domains of social cognition, neurocognition, resilience and real-life

functioning were spatially contiguous and highly interconnected, regardless of the use of one or more measures of the same construct. Psychopathological variables had a less interconnected pattern, with avolition/expressive deficit on one side of real-life functioning nodes, and positive/disorganization nodes on the opposite side.

A closer look at the two networks revealed some changes, in particular for the service engagement node, that appeared more interconnected at follow-up than at baseline, as it acquired direct connections with all real-life domains, and with one node of the social cognition (MSCEIT). It is also worth mentioning that, in the follow-up network, besides the indirect connection through the functional capacity, one of the social cognition nodes (FEIT) acquired a direct connection with one of the real-life functioning nodes (work skills), and a neurocognition node (processing speed) established a direct connection with the everyday life skills node.

These direct connections between cognition nodes and real-life functioning domains were not observed in our previous study including 921 subjects[10], and were not detected in the present study at baseline; in both cases, we only found an indirect connection through functional capacity. We might hypothesize that the emergence of these direct links reflects the slight improvements observed in social cognition and neurocognition variables. However, current data do not allow firm conclusions in this respect.

All centrality measures were similar across the two time points. Work skills represented the only exception, as it showed a higher centrality at follow-up, in particular in terms of betweenness. This might be explained by the newly established link with the cognition area, through social cognition, that at baseline was linked to the real-functioning domains only through functional capacity, while at follow-up acquired a direct connection with work skills through FEIT.

We also observed an increased strength for service engagement at follow-up, reflecting its higher number of connections with other nodes, and a decreased betweenness of functional capacity, probably because neurocognitive and social cognition variables established direct connections with real-life functioning domains. The increased centrality of service engagement might be due to the fact that more collaborative and treatment adherent patients were more likely to join the follow-up study.

In a population of chronic patients, the good degree of stability of the network structure after a 4-year follow-up confirms the robustness of the baseline findings and supports the stability and replicability of network analyses. We believe that this finding is important, in the light of some recent criticisms to the network analysis approach[37,38].

In the light of the focus of the Italian Network for Research on Psychoses on the variables that influence real-life functioning and recovery in schizophrenia, the other important goal of the study was to compare the network structure of recovered versus non-recovered subjects. We found significant differences between the networks of the two groups, in terms of number and strengths of connections. In fact, differently from non-recovered patients, recovered patients have a very sparse network, with real-life functioning and psychopathology nodes disconnected, in most cases, from the remaining nodes.

This finding is consistent with data reported by van Rooijen et al[12], who found that the network observed in remitted psychotic patients had fewer connections than that found in non-remitted subjects. It is also in line with the study by van Borkulo et al[11], who reported that depressed patients showing persistent symptoms at 2-year follow-up exhibited a more densely connected network at baseline than remitters.

All these findings are consistent with the network theory assumption that a strongly interconnected network, possibly due to tightly coupled symptoms/dysfunctions that tend to maintain each other's activation, might play an important role in the persistence of mental disorder[39]. Our data also suggest that the same mechanism may drive the poor functional outcome of the disorder.

The present study has many strengths, in particular the large sample size and the assessment of variables that are core aspects of the recovery process, in addition to the traditional psychopathological ones. However, the relatively small size of the recovered subgroup requires replication in a larger sample.

In conclusion, in our follow-up study, the network structure did not change significantly from baseline in the overall sample and in non-recovered patients. Functional capacity and everyday life skills had high betweenness and closeness, as they had at baseline, whereas psychopathological variables remained more peripheral. However, the network structure was very different in recovered subjects, in which we found few connections only. Early and integrated treatment plans, targeting variables with high centrality, might prevent the emergence of self-reinforcing networks of symptoms/dysfunctions in people with schizophrenia.

APPENDIX

Members of the Italian Network for Research on Psychoses who participated in this study include: Francesco Catapano, Giuseppe Piegari, Carmen Aiello, Francesco Brando, Luigi Giuliani, Daria Pietrafesa (University of Campania "Luigi Vanvitelli", Naples); Marco Papalino, Giovanni Mercadante, Piergiuseppe Di Palo (University of Bari); Stefano Barlati, Giacomo Deste, Paolo Valsecchi (University of Brescia); Federica Pinna, Benedetta Olivieri, Daniela Manca (University of Cagliari); Maria Salvina Signorelli, Laura Fusar Poli (University of Catania); Domenico De Berardis, Silvia Fraticelli, Mariangela Corbo (University of Chieti); Stefano Pallanti (University of Florence); Mario Altamura, Raffaella Carnevale, Stefania Malerba (University of Foggia); Pietro Calcagno, Domenico Zampogna, Alessandro Corso (University of Genoa); Laura Giusti, Anna Salza, Donatella Ussorio, Dalila Talevi, Valentina Socci, Francesca Pacitti (University of L'Aquila); Andrea de Bartolomeis (University of Naples Federico II); Carla Gramaglia, Eleonora Gambaro, Eleonora Gattoni (University of Eastern Piedmont, Novara); Angela Favaro, Elena Tenconi, Paolo Meneguzzo (University of Padua); Matteo Tonna, Paolo Ossola, Maria Lidia Gerra (University of Parma); Claudia Carmassi, Ivan Cremone, Barbara Carpita (University of Pisa); Nicoletta Girardi, Marianna Frascarelli, Antonio Buzzanca, Roberto Brugnoli, Anna Comparelli, Valentina Corigliano (Sapienza University of Rome); Giorgio Di Lorenzo, Cinzia Niolu, Michele Ribolsi (Tor Vergata University of Rome); Giulio Corrivetti, Giammarco Cascino, Gianfranco del Buono (Department of Mental Health, Salerno); Simone Bolognesi, Andrea Fagiolini, Arianna Goracci (University of Siena); Silvio Bellino, Cristiana Montemagni, Claudio Brasso (University of Turin).

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A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression

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No network meta-analysis has examined the relative effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression, while this is a very important clinical issue. We conducted systematic searches in bibliographical databases to identify randomized trials in which a psychotherapy and a pharmacotherapy for the acute or long-term treatment of depression were compared with each other, or in which the combination of a psychotherapy and a pharmacotherapy was compared with either one alone. The main outcome was treatment response (50% improvement between baseline and endpoint). Remission and acceptability (defined as study drop-out for any reason) were also examined. Possible moderators that were assessed included chronic and treatment-resistant depression and baseline severity of depression. Data were pooled as relative risk (RR) using a random-effects model. A total of 101 studies with 11,910 patients were included. Depression in most studies was moderate to severe. In the network meta-analysis, combined treatment was more effective than psychotherapy alone (RR=1.27; 95% CI: 1.14-1.39) and pharmacotherapy alone (RR=1.25; 95% CI: 1.14-1.37) in achieving response at the end of treatment. No significant difference was found between psychotherapy alone and pharmacotherapy alone (RR=0.99; 95% CI: 0.92-1.08). Similar results were found for remission. Combined treatment (RR=1.23; 95% CI: 1.05-1.45) and psychotherapy alone (RR=1.17; 95% CI: 1.02-1.32) were more acceptable than pharmacotherapy. Results were similar for chronic and treatment-resistant depression. The combination of psychotherapy and pharmacotherapy seems to be the best choice for patients with moderate depression. More research is needed on long-term effects of treatments (including cost-effectiveness), on the impact of specific pharmacological and non-pharmacological approaches, and on the effects in specific populations of patients.

Key words: Depression, psychotherapy, pharmacotherapy, combined treatment, cognitive behavior therapy, interpersonal therapy, antidepressants, acceptability, chronic depression, treatment-resistant depression, network meta-analysis

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Mental disorders are a major cause of global health burden, accounting for 23% of years lived with disability[1]. With 350 million people affected in the world, depressive disorder is the second leading cause of global burden[2]. The high direct and indirect costs of major depression are substantially due to significant deficits in treatment provision[3]. There are a number of efficacious interventions for depressive disorder, and the key challenge is how best to implement currently available effective treatments[4].

It is well-established that psychotherapies and pharmacological therapies are effective in the treatment of adult depression. Psychotherapies have shown superior effects compared to control conditions in numerous clinical trials. Moreover, different psychotherapeutic types – e.g., cognitive behavior therapy (CBT) and interpersonal therapy – have comparable outcomes in depression[5]. Another large body of research has shown that different classes of antidepressants are effective in the treatment of depression[6], including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and several others.

Although the absolute effectiveness of psychotherapies and pharmacotherapies is well documented, the evidence supporting their relative effects remains inconclusive. Conventional meta-analyses of trials directly comparing psychotherapies and pharmacotherapies have suggested that, as classes of treatments, they have comparable effects, with no or only minor differences[7,8], although there may be some influence of placebo effects[9], sponsorship bias[10], and possibly the superiority of some medications over others[6]. Other pairwise meta-analyses have found that the combination of psychotherapy and pharmacotherapy may be more effective than either of these alone[11,12], although the evidence is not conclusive[13,14]. Moreover, some studies suggest that the two monotherapies result in differential effects over long-term follow-ups, with psychotherapy having enduring effects on depression when pharmacotherapy is discontinued.

Several issues regarding the differential effects of combined treatment, psychotherapies and pharmacotherapies remain unsolved. Existing meta-analyses have compared only two interventions at a time: psychotherapy vs. pharmacotherapy[15], combined treatment vs. psychotherapy[14], and combined treatment vs. pharmacotherapy[11,12]. To get a better understanding of the relative effectiveness of these treatments, it is necessary to combine direct and indirect evidence from all clinical trials. Network meta-analyses can combine multiple comparisons in one analysis, are able to use direct and indirect evidence, and thus make optimal use of all available evidence. These analyses consequently make better estimates of the differences between treatments, have more statistical power to examine moderators of outcome, and can present consolidated comparisons among alternative treatments[16].

Further important questions have not yet been answered. The majority of randomized trials in this field may be prone to methodological bias; no information is available for different populations of patients (e.g., mild vs. chronic or treatment-resistant depression); and acceptability of the treatments has not been examined extensively so far.

We therefore conducted a network meta-analysis based on randomized trials in which a psychotherapy and a pharmacotherapy for depression were compared with each other, or in which the combination of a psychotherapy and a pharmacotherapy was compared with either one alone.

METHODS

Identification and selection of studies

The protocol for this network meta-analysis was registered at PROSPERO (CRD42018114961). For the identification of studies, we used a database of randomized trials examining the effects of psychotherapies in depression, that was developed through a comprehensive literature search (from 1966 to January 1, 2018)[17]. Four major bibliographical databases (PubMed, PsycINFO, EMBASE and the Cochrane Library) were searched by combining index and text words indicative of depression and psychotherapies, with filters for randomized controlled trials. All records and full texts were screened by two independent researchers. Any disagreement was solved through discussion.

We included studies in which a psychotherapy and a pharmacological treatment for depression were directly compared with each other, and studies in which the combination of a psychotherapy and a pharmacological treatment was compared with either one alone. When these trials included pill placebo or the combination of psychotherapy and pill placebo, we included such arms as well.

We defined psychotherapy as "the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions and/or other personal characteristics in directions that the participants deem desirable"[18]. We allowed any type of psychotherapy[8] in any delivery format (individual, group, face-to-face, telephone, or self-help including Internet) and any type of oral antidepressant treatment within the therapeutic dose range.

We only included studies recruiting patients with acute depressive disorder according to modern operationalized and validated criteria. Comorbid mental or somatic disorders were not excluded. We did not set a maximum or minimum concerning the length of treatment or the duration of follow-up[7].

When a study contained two or more arms to be included in the same node (for example, when one study compared two types of psychotherapy with one pharmacotherapy condition), we considered them as separate comparisons and subdivided the comparisons appropriately in order to avoid double counting[19]. We also conducted sensitivity analyses in which the two comparable arms were pooled into one arm.

Risk of bias and data extraction

Two independent researchers assessed the risk of bias of included studies using four criteria of the Cochrane tool[20]. Disagreements were solved through discussion. Pharmacotherapy studies were also assessed regarding the use of therapeutic dose[6] and the titration schedule (i.e., therapeutic dose achieved within three weeks). The pharmacotherapy was deemed adequate if both criteria were met. Psychotherapies were assessed with respect to using a treatment manual, provision of therapy by specially trained therapists, and verification of treatment integrity[21,22].

We also coded participant characteristics (type of depressive disorder, recruitment method, target group); the type of psychotherapy and the number of treatment sessions; the type of medication; whether or not a placebo condition was included in the trial (because then patients were blinded for medication or placebo)[9]; the time between pre-test and post-test (in weeks); and the country where the study was conducted.

Outcome measures

Treatment response, defined as a 50% reduction in depressive symptomatology according to a standardized rating scale, was chosen as the primary outcome. When not reported, we imputed response rate using a validated method[23]. The timepoint for the primary outcome was the end of the therapy. We also calculated response rates at follow-up of 6 months, between 6 and 12 months, and more than 12 months.

Remission rate was defined as the number of patients with a score for depressive symptoms below a specific cut-off on a validated rating scale. We also calculated the standardized mean difference (SMD) between pairs of conditions, expressing the size of the intervention effect in each study relative to the variability observed in that study. Acceptability of the treatment formats was operationalized as study drop-out for any reason during the acute phase treatment.

Meta-analyses

We conducted pairwise meta-analyses for all comparisons, using a random effects pooling model. To quantify heterogeneity, we calculated the I^2 statistic with 95% confidence intervals (CIs), using the non-central chi-squared-based approach within the heterogi module for Stata[24]. We tested for small study effects, including publication bias, with Egger's test[25].

The comparative effectiveness was evaluated using the network meta-analysis methodology. First, we summarized the geometry of the network of evidence using network plots for the main outcome[26]. Second, we conducted contrast-based analyses to

assess comparative efficacy and acceptability[27]. Given the expected clinical and methodological heterogeneity of treatment effects among the studies, we adopted the multivariate random effect models[28]. Relative risks (RRs) and SMDs were reported with their 95% CIs. The ranking of treatment formats was estimated according to the "surface under the cumulative ranking" (SUCRA), based on the estimated multivariate random effects models[26]. We checked the consistency of the network using tests of local and global inconsistency[29,30].

Further analyses

We conducted separate pairwise and network meta-analyses for studies examining chronic or treatment-resistant depression. We also selected studies that reported the baseline score on the Hamilton Depression Rating Scale (HAM-D)[31] and examined in a meta-regression analysis whether baseline severity was associated with outcome. We then conducted separate pairwise and network meta-analyses for mild, moderate and severe depression according to the baseline severity of the sample, using the thresholds proposed by Zimmerman et al[32]. In addition, we performed a multivariate meta-regression analysis to examine possible sources of heterogeneity.

We carried out a series of sensitivity analyses with studies in which pharmacotherapy was optimized; those in which psychotherapy met all the above-mentioned quality criteria; those at low risk of bias; and those in which no placebo was included. A sensitivity analysis was also conducted in which all patients randomized to different arms in the same node (e.g., two types of psychotherapy) in a given study were pooled, so that there was only one arm for each condition.

All analyses were conducted in Stata/SE 14.2.

RESULTS

Studies included and their characteristics

After examining a total of 19,982 abstracts (15,598 after removal of duplicates), we retrieved 2,323 full-text papers for further consideration. The PRISMA flow chart describing the inclusion process is presented in Figure 1. A total of 101 studies met inclusion criteria (11,910 participants overall: 2,587 randomized to combined treatment, 3,625 to psychotherapy, 4,769 to pharmacotherapy, 632 to placebo and 297 to psychotherapy plus placebo)[33-133].

Selected characteristics of the included studies are summarized in Table 1. In 12 studies two types of psychotherapy were examined as separate arms; in one study two types of pharmacotherapy were included[62]; and in one other study the therapy was separated into two arms with different providers (general practitioners or nurses)[105]. In total, 115 comparisons were available in the studies.

The aggregated characteristics of the included studies are presented in Table 2. In brief, 47 trials recruited patients exclusively from clinical samples, and 75 were aimed at unselected adults. Thirteen studies were aimed at patients with chronic or treatment-resistant depression. CBT was the most commonly used psychotherapy (48 trials); an individual format was used in 81 psychotherapy studies; 45 trials met all three quality criteria. SSRIs were the most frequently used medications; pharmacotherapy was judged adequate in 67 trials. The time from pre- to post-test ranged from 4 to 36 weeks, with the majority of comparisons (78%) ranging from 8 to 16 weeks. In 36 of 51 trials reporting the mean baseline HAM-D score, the severity of depression was moderate.

There was moderate to high risk of bias in most trials. A total of 48 studies reported an adequate sequence generation; 40 reported allocation to conditions by an independent (third) party; and 81 reported blinding of outcome assessors or used only self-report outcomes. Intention-to-treat analyses were conducted in 58 studies. Twenty-three studies met all four quality criteria (28 when self-report was rated as low risk of bias), 19 met three criteria, another 19 met two criteria, and the remaining 40 studies met one or none of the criteria.

Meta-analyses

Table 3 shows the main results of the pairwise meta-analyses for the response rates. Combined treatment was more effective than both psychotherapy alone (RR=1.25, 95% CI: 1.09-1.43) and pharmacotherapy alone (RR=1.27, 95% CI: 1.12-1.43). The difference between psychotherapy alone and pharmacotherapy alone was not significant (RR=0.98, 95% CI: 0.91-1.06). Heterogeneity was low to moderate in most comparisons. In the comparisons with more than 10 studies, only heterogeneity of combined treatment versus pharmacotherapy was higher than 50%. Egger's test was only significant for combined treatment versus pharmacotherapy (p=0.02) and for combined treatment versus psychotherapy plus placebo (p=0.02).

The network for response rates is graphically represented in Figure 2. The main results of the network meta-analysis are presented in Table 3. Combined treatment was superior to either psychotherapy alone or pharmacotherapy alone in terms of response (RR=1.27, 95% CI: 1.14-1.39, and RR=1.25, 95% CI: 1.14-1.37, respectively), remission (RR=1.22, 95% CI: 1.08-1.39 and RR=1.23, 95% CI: 1.09-1.39), and SMD (0.30, 95% CI: 0.14-0.45 and 0.33, 95% CI: 0.20-0.47). No significant difference was found between psychotherapy alone and pharmacotherapy alone concerning response (RR=0.99, 95% CI: 0.92-1.08), remission (RR=1.01, 0.93-1.10), and SMD (SMD=0.04, 95% CI: –0.09 to 0.16). Acceptability was significantly better for combined treatment compared with pharmacotherapy (RR=1.23, 95% CI: 1.05-1.45), as well as for psychotherapy compared with pharmacotherapy (RR=1.17, 95% CI: 1.02-1.32).

In the relatively few relevant studies included in the network meta-analysis, response rate was significantly higher for combined treatment compared to psychotherapy plus pill placebo (RR=1.30, 95% CI: 1.06-1.59) and for combined treatment com-

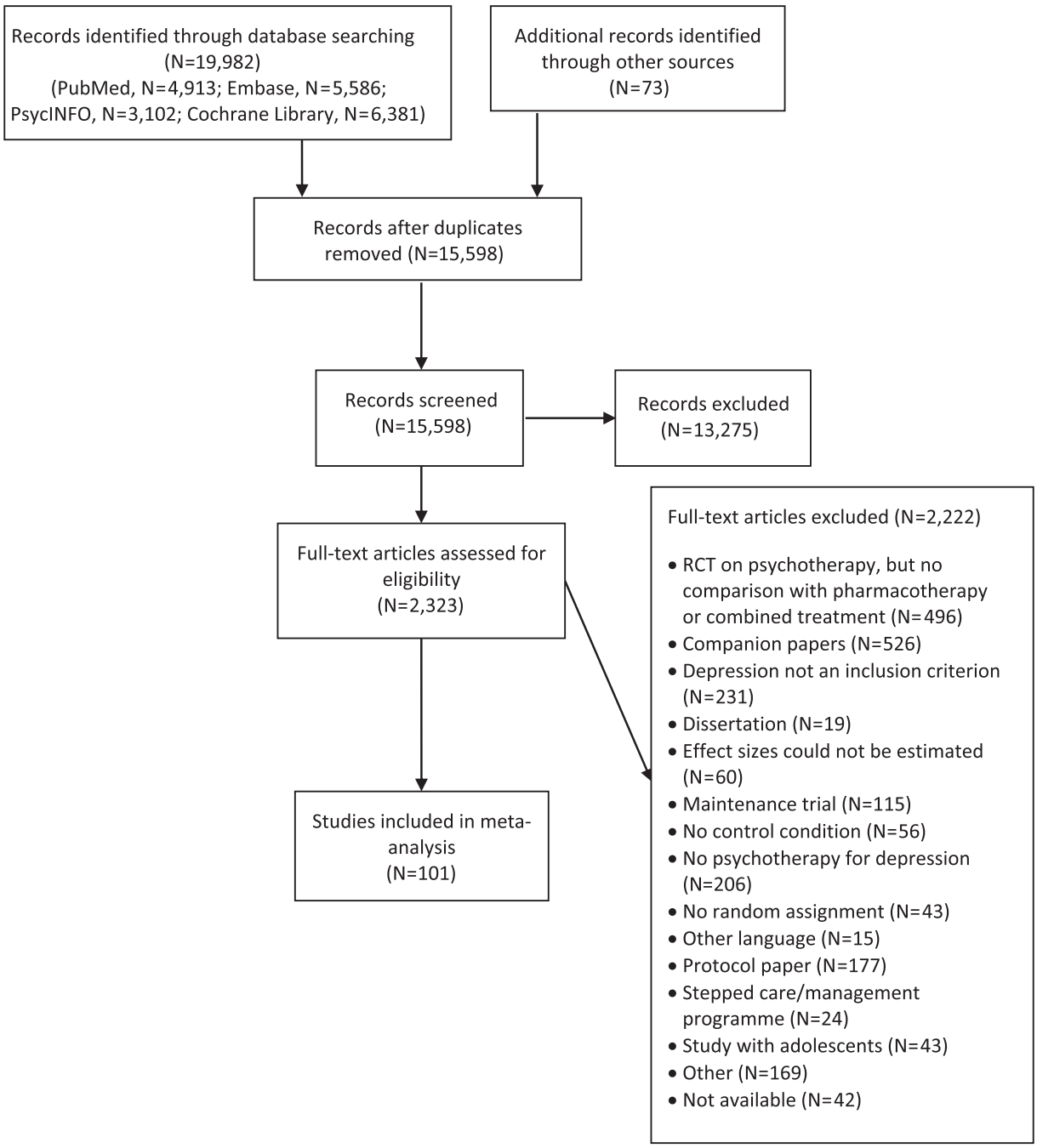

Figure 1 Flow chart for inclusion of studies. RCT – randomized clinical trial

pared to pill placebo (RR=1.47, 95% CI: 1.20-1.75). Remission rate was significantly higher for combined treatment compared to pill placebo (RR=1.59, 95% CI: 1.27-2.00). Combined treatment also resulted in a significantly higher SMD than pill placebo (0.43, 95% CI: 0.10-0.76).

The consistency of the network was examined using the loop-specific approach. No inconsistency factors were found to be significant, although this cannot be considered as evidence for the absence of inconsistency, because of low power in some of the loops, especially in the presence of large heterogeneity in pairwise comparisons. The design-by-treatment interaction model did not indicate global inconsistency in the network (X^2=10.51, df=10, p for the null hypothesis of consistency in the network: 0.40).

In the SUCRA analyses, combined treatment ranked clearly best for response (99.9), remission (93.0) and SMD (95.6), as well as for acceptability (78.7). Psychotherapy ranked better than pharmacotherapy for remission (45.0 vs. 40.8), SMD (43.5 vs.

Table 1 Characteristics of included studies

Study	Conditions	Psychotherapy	Therapy quality	Pharmacotherapy	Adequate therapy	Risk of bias
Ahmadpanah et al[33]	Combined vs. pharmacotherapy	MBCT	– – –	SSRI	Yes	+ + + +
	Combined vs. pharmacotherapy	Stress management	– – –	SSRI	Yes	+ + + +
Altamura et al[34]	Psychotherapy vs. pharmacotherapy	IPT	+ + –	SSRI	Yes	+ – + –
Appleby et al[35]	Combined vs. pharmacotherapy vs. placebo vs. psychotherapy + placebo	CBT	– + –	SSRI	No	+ – + +
Ashouri et al[36]	Combined vs. pharmacotherapy	CBT	– – –	Other	No	– – sr –
	Combined vs. pharmacotherapy	MBCT	– – –	Other	No	– – sr –
Barber et al[37]	Psychotherapy vs. pharmacotherapy vs. placebo	DYN	+ + –	Other	Yes	+ – + +
Barrett et al[38]	Psychotherapy vs. pharmacotherapy vs. placebo	PST	+ + –	SSRI	Yes	+ – + –
Beck et al[39]	Combined vs. psychotherapy	CBT	+ + –	TCA	Yes	– – – –
Bedi et al[40]	Psychotherapy vs. pharmacotherapy	Not specified	– + –	Other	No	– + sr –
Bellack et al[41]	Combined vs. pharmacotherapy vs. psychotherapy + placebo	Social skills	+ + –	TCA	Yes	– – + –
Bellino et al[42]	Combined vs. pharmacotherapy	IPT	+ + –	SSRI	Yes	– – + –
Blackburn et al[43]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	– – –	TCA	Yes	– – – –
Blackburn & Moore[44]	Psychotherapy vs. pharmacotherapy	CBT	– + –	Other	No	– – + –
Bloch et al[45]	Combined vs. psychotherapy + placebo	DYN	– + +	SSRI	Yes	+ + + +
Blom et al[46]	Combined vs. psychotherapy vs. pharmacotherapy vs. psychotherapy + placebo	IPT	+ + +	Other	Yes	– – + +
Browne et al[47]	Combined vs. psychotherapy vs. pharmacotherapy	IPT	+ + +	SSRI	Yes	+ + + –
Burnand et al[48]	Combined vs. pharmacotherapy	DYN	– + +	Other	Yes	– – + –
Chibanda et al[49]	Psychotherapy vs. pharmacotherapy	PST	+ + +	TCA	No	+ – sr –
Corruble et al[50]	Combined vs. pharmacotherapy	Social rhythms	+ + +	Other	No	+ + + –
Covi & Lipman[51]	Combined vs. psychotherapy	CBT	+ + +	TCA	Yes	– – sr –
David et al[52]	Psychotherapy vs. pharmacotherapy	CT	+ + +	SSRI	Yes	– – + +
	Psychotherapy vs. pharmacotherapy	REBT	+ + +	SSRI	Yes	– – + +
De Jonghe et al[53]	Combined vs. pharmacotherapy	DYN	+ + +	Other	No	– – + +
De Jonghe et al[54]	Combined vs. psychotherapy	DYN	+ + +	Other	No	– – + –
de Mello et al[55]	Combined vs. pharmacotherapy	IPT	+ + –	Other	Yes	– – + –
Dekker et al[56]	Psychotherapy vs. pharmacotherapy	DYN	+ + +	Other	No	– – + –
Denton et al[57]	Combined vs. pharmacotherapy	EFT	+ + +	Other	No	+ + + +
DeRubeis et al[58]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	– – + +
Dimidjian et al[59]	Psychotherapy vs. pharmacotherapy	BAT	+ + +	SSRI	Yes	+ – + +
	Psychotherapy vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	+ – + +
Dozois et al[60]	Combined vs. pharmacotherapy	CBT	+ + +	Other	No	– + – –
Dunlop et al[61]	Psychotherapy vs. pharmacotherapy	CBT	+ – –	SSRI	Yes	– + + –
Dunlop et al[62]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	Other	Yes	+ + + +
	Psychotherapy vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	+ + + +
Dunn[63]	Combined vs. pharmacotherapy	CBT	– – –	Other	No	– – sr –
Dunner et al[64]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	– – + –
Eisendrath et al[65]	Combined vs. pharmacotherapy	MBCT	+ + +	Other	No	+ + + +
Elkin et al[66]	Psychotherapy vs. pharmacotherapy vs. placebo	CBT	+ + +	TCA	Yes	+ + + +
	Psychotherapy vs. pharmacotherapy vs. placebo	IPT	+ + +	TCA	Yes	+ + + +

Table 1 Characteristics of included studies (*continued*)

Study	Conditions	Psychotherapy	Therapy quality	Pharmacotherapy	Adequate therapy	Risk of bias
Faramarzi et al[67]	Psychotherapy vs. pharmacotherapy	CBT	+ – –	SSRI	Yes	– – sr –
Finkenzeller et al[68]	Combined vs. psychotherapy vs. pharmacotherapy	IPT	+ – –	SSRI	Yes	+ – + +
Frank et al[69]	Psychotherapy vs. pharmacotherapy	IPT	+ + +	SSRI	Yes	– – + +
Gater et al[70]	Combined vs. psychotherapy vs. pharmacotherapy	Social group	+ + +	Other	No	+ + + +
Gaudiano et al[71]	Combined vs. pharmacotherapy	ABT	+ + +	Other	No	– – + +
Hautzinger et al[72]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	– – –	TCA	Yes	– – + +
Hegerl et al[73]	Psychotherapy vs. pharmacotherapy vs. placebo	CBT	+ – +	SSRI	Yes	+ + + +
Hellerstein et al[74]	Combined vs. pharmacotherapy	Cognitive-interpersonal	+ + +	SSRI	Yes	– – – +
Hollon et al[75]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	+ + +	TCA	Yes	– – + +
Hollon et al[76]	Combined vs. pharmacotherapy	CBT	+ + +	Other	No	+ + + +
Hsiao et al[77]	Combined vs. pharmacotherapy	BMS	+ + –	Other	No	+ – sr +
Husain et al[78]	Psychotherapy vs. pharmacotherapy	CBT	+ – –	Other	No	+ + + +
Jarrett et al[79]	Psychotherapy vs. pharmacotherapy vs. placebo	CBT	+ + +	Other	Yes	– + + +
Keller et al[80]	Combined vs. psychotherapy vs. pharmacotherapy	CBASP	+ + +	Other	Yes	+ + + +
Kennedy et al[81]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	Other	Yes	– – – –
Lam et al[82]	Combined vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	+ + + +
Lesperance et al[83]	Combined vs. pharmacotherapy vs. placebo vs. psychotherapy + placebo	IPT	+ + +	SSRI	Yes	+ + + +
Lynch et al[84]	Combined vs. pharmacotherapy	DBT	– + +	Other	No	– – – –
Macaskill & Macaskill[85]	Combined vs. pharmacotherapy	CBT	+ – –	TCA	Yes	– – – –
Maina et al[86]	Combined vs. pharmacotherapy	DYN	– + +	SSRI	Yes	+ + + +
Maldonado López[87]	Psychotherapy vs. pharmacotherapy	CBT	– – –	Other	No	– – + –
	Psychotherapy vs. pharmacotherapy	BAT	– – –	Other	No	– – + –
Maldonado López [88]	Combined vs. pharmacotherapy	CBT	– – –	Other	No	– – + –
	Combined vs. pharmacotherapy	BAT	– – –	Other	No	– – + –
Markowitz et al[89]	Combined vs. psychotherapy	SUP	+ + +	TCA	Yes	+ + + +
Markowitz et al[90]	Combined vs. psychotherapy vs. pharmacotherapy	IPT	+ + +	SSRI	Yes	+ + + +
	Psychotherapy vs. pharmacotherapy	SUP	+ + +	SSRI	Yes	+ + + +
Marshall et al[91]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	Other	No	– – – –
	Psychotherapy vs. pharmacotherapy	IPT	+ + +	Other	No	– – – –
Martin et al[92]	Psychotherapy vs. pharmacotherapy	IPT	+ + –	Other	Yes	– – – +
McKnight et al[93]	Psychotherapy vs. pharmacotherapy	CBT	+ + –	TCA	No	– – sr –
McLean & Hakstian[94]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	TCA	Yes	– – sr –
	Psychotherapy vs. pharmacotherapy	DYN	+ + +	TCA	Yes	– – sr –
Menchetti et al[95]	Psychotherapy vs. pharmacotherapy	IPT	+ – –	SSRI	No	+ + – +
Milgrom et al[96]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	+ – +	SSRI	Yes	+ + sr +
Miranda et al[97]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	Other	No	+ + + +
Misri et al[98]	Combined vs. pharmacotherapy	CBT	+ + –	SSRI	No	+ – + +
Mitchell et al[99]	Combined vs. pharmacotherapy	PST	+ – +	Other	No	+ + + +
Mohr et al[100]	Psychotherapy vs. pharmacotherapy	CBT	+ – +	SSRI	Yes	– – – +
	Psychotherapy vs. pharmacotherapy	SEG	+ – +	SSRI	Yes	– – – +
Moradveisi et al[101]	Psychotherapy vs. pharmacotherapy	BAT	+ + +	SSRI	Yes	+ + + +

Table 1 Characteristics of included studies (*continued*)

Study	Conditions	Psychotherapy	Therapy quality	Pharmacotherapy	Adequate therapy	Risk of bias
Murphy et al[102]	Combined vs. psychotherapy vs. pharmacotherapy vs. psychotherapy + placebo	CBT	+ + +	TCA	Yes	+ + – +
Murphy et al[103]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	TCA	Yes	+ – – –
Mynors-Wallis et al[104]	Psychotherapy vs. pharmacotherapy vs. placebo	PST	+ + –	TCA	Yes	– + + –
Mynors-Wallis et al[105]	Psychotherapy vs. pharmacotherapy	PST	+ – +	SSRI	Yes	+ + + +
	Combined vs. psychotherapy vs. pharmacotherapy	PST	+ – +	SSRI	Yes	+ + + +
Naeem et al[106]	Combined vs. pharmacotherapy	CBT	+ + +	SSRI	Yes	+ + sr +
Parker et al[107]	Psychotherapy vs. pharmacotherapy	CBT	+ + –	Other	Yes	+ + + –
Petrak et al[108]	Psychotherapy vs. pharmacotherapy	CBT	+ + –	SSRI	Yes	+ + + +
Quilty et al[109]	Psychotherapy vs. pharmacotherapy	CBT	+ + +	Other	No	– – – +
Ravindran et al[110]	Combined vs. pharmacotherapy vs. placebo vs. psychotherapy + placebo	CBT	+ + –	SSRI	Yes	+ + + –
Reynolds et al[111]	Combined vs. pharmacotherapy vs. placebo vs. psychotherapy + placebo	IPT	+ + +	TCA	Yes	– – + +
Rodriguez Vega et al[112]	Combined vs. pharmacotherapy	Narrative	+ + +	SSRI	Yes	+ + sr +
Roth et al[113]	Combined vs. psychotherapy	Self-control	+ + +	TCA	Yes	– – – –
Rush et al[114]	Psychotherapy vs. pharmacotherapy	CBT	+ – +	TCA	Yes	– – + +
Rush & Watkins[115]	Combined vs. psychotherapy	CBT	+ – +	Other	No	– – sr +
Salminen et al[116]	Psychotherapy vs. pharmacotherapy	DYN	– + –	SSRI	Yes	– – – +
Schiffer & Wineman[117]	Combined vs. psychotherapy + placebo	Three types	– – –	TCA	Yes	– – – –
Schramm et al[118]	Psychotherapy vs. pharmacotherapy	CBASP	+ + +	SSRI	Yes	+ – + +
Schulberg et al[119]	Psychotherapy vs. pharmacotherapy	IPT	+ + +	TCA	Yes	– – + +
Scott & Freeman[120]	Psychotherapy vs. pharmacotherapy	CBT	+ + –	TCA	Yes	– + + –
	Psychotherapy vs. pharmacotherapy	SUP	– – –	TCA	Yes	– + + –
Shamsaei et al[121]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	– – –	SSRI	Yes	+ – sr –
Sharp et al[122]	Psychotherapy vs. pharmacotherapy	SUP	– + +	Other	No	+ + sr +
Souza et al[123]	Combined vs. pharmacotherapy	IPT	+ + +	Other	No	+ + + +
Stravynski et al[124]	Combined vs. psychotherapy	CBT	– – –	TCA	Yes	– – + –
Targ et al[125]	Combined vs. psychotherapy + placebo	PST	– – +	SSRI	Yes	– – + –
Thompson et al[126]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	+ – –	TCA	No	– – – +
Weissman et al[127]	Combined vs. psychotherapy vs. pharmacotherapy	IPT	+ – –	TCA	Yes	– – + –
Wiles et al[128]	Combined vs. pharmacotherapy	CBT	+ – +	Other	No	+ + sr +
Wiles et al[129]	Combined vs. pharmacotherapy	CBT	+ + +	Other	No	+ + sr +
Williams et al[130]	Psychotherapy vs. pharmacotherapy vs. placebo	PST	+ + –	SSRI	Yes	+ + + +
Wilson[131]	Combined vs. pharmacotherapy vs. placebo vs. psychotherapy + placebo	BAT	+ – –	TCA	Yes	– – + –
Zisook et al[132]	Combined vs. psychotherapy + placebo	SUP	– – –	SSRI	Yes	– – + +
Zu et al[133]	Combined vs. psychotherapy vs. pharmacotherapy	CBT	– + +	SSRI	Yes	+ – + –

Risk of bias: + means low risk, – means high or unclear risk, "sr" means that only a self-report instrument was used
ABT – acceptance-based behavior therapy, BAT – behavioral activation therapy, BMS – body-mind-spirit therapy, CBASP – cognitive behavioral analysis system of psychotherapy, CBT – cognitive behavior therapy, CT – cognitive therapy, DBT – dialectical behavioral therapy, DYN – psychodynamic therapy, EFT – emotion-focused therapy, IPT – interpersonal psychotherapy, MBCT – mindfulness-based cognitive therapy, PST – problem-solving therapy, REBT – rational-emotive behavior therapy, SEG – supportive-expressive group psychotherapy, SUP – supportive therapy, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant

Table 2 Description of included studies and distribution of potential effect modifiers

		All studies		Combined vs. psychotherapy		Combined vs. pharmacotherapy		Psychotherapy vs. pharmacotherapy	
		N	%	N	%	N	%	N	%
Patients									
Recruitment	Community	35	34.7	9	40.9	14	29.2	21	36.8
	Clinical	47	46.5	11	50.0	28	58.3	26	45.6
	Other	19	18.8	2	9.1	6	12.5	10	17.5
Target group	Adults	75	74.3	17	77.3	33	68.8	46	80.7
	Specific group	26	25.7	5	22.7	15	31.3	11	19.3
Chronic or treatment-resistant depression		13	12.9	3	13.6	11	22.9	5	8.8
Psychotherapy									
Type	CBT	48	47.5	12	54.5	21	43.8	31	54.4
	Other	52	52.5	10	45.5	27	56.3	26	45.6
Format	Individual	81	80.2	15	68.2	38	79.2	47	82.5
	Group/mixed	20	19.8	7	31.8	10	20.8	10	17.5
Optimized		45	44.6	11	50.0	22	45.8	26	45.6
Pharmacotherapy									
Type	SSRI	38	37.6	6	27.3	17	35.4	24	42.1
	TCA	26	25.7	11	50.0	11	22.9	15	26.3
	Other	37	36.6	5	22.7	20	41.7	18	31.6
Optimized		67	66.3	18	81.8	28	58.3	43	75.4
General study characteristics									
Country	US	53	52.5	14	63.6	23	47.9	29	50.9
	Europe	32	31.7	5	22.7	15	31.3	20	35.1
	Other	16	15.8	3	13.6	10	20.8	8	14.0
Low risk of bias		28	27.7	5	22.7	17	35.4	13	22.8

CBT – cognitive behavior therapy, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant

29.1) and acceptability (63.2 vs. 17.4), whereas pharmacotherapy ranked better than psychotherapy for response (54.2 vs. 49.6).

Further analyses

The results of the sensitivity analyses are reported in Table 4. The main outcomes were comparable across all analyses, with combined treatment being superior to psychotherapy or pharmacotherapy alone, and no significant difference between psychotherapy and pharmacotherapy.

We conducted separate pairwise and network meta-analyses limited to studies on chronic or treatment-resistant depression (only for response), whose results are presented in Table 5. Although the number of studies was relatively small, the findings were comparable to the main analyses, with superior effects for combined treatment versus psychotherapy or pharmacotherapy alone (RR=1.59, 95% CI: 1.23-2.04 and RR=1.39, 95% CI: 1.15-1.67), and comparable effects for psychotherapy and pharmacotherapy (RR=0.87, 95% CI: 0.68-1.10).

In the meta-regression analysis including the studies that reported the baseline severity of depression on the HAM-D, this severity was not associated with response rate in the combined treatment versus psychotherapy comparison (coefficient=–0.2, SE=0.02, p=0.29) or in the combined versus pharmacotherapy comparison (coefficient=–0.02, SE=0.2, p=0.13).

We also conducted separate network meta-analyses for mild, moderate and severe depression (Table 5). In severe depression, combined treatment was more effective than pharmacotherapy alone (RR=1.45, 95% CI: 1.10-1.89), while there were only two comparisons of combined treatment with psychotherapy alone. In moderate depression, combined treatment was more effective than either psychotherapy or pharmacotherapy alone (RR=1.19, 95% CI: 1.05-1.37, and RR=1.23, 95% CI: 1.09-1.41), and there was no significant difference between psychotherapy and pharmacotherapy (RR=1.03, 95% CI: 0.94-1.14). Unfortunately, there were too few studies in patients with mild depression.

In the multivariate meta-regression analysis conducted to examine possible sources of heterogeneity, with response as outcome and with the three main nodes (combined treatment,

Table 3 Results of pairwise and network meta-analyses

	Pairwise meta-analyses						Network meta-analysis	
	N	RR	95% CI	I^2	95% CI	Egger	RR	95% CI
Response								
Combined vs. psychotherapy	19	**1.25**	1.09-1.43	44	0-66	0.36	**1.27**	1.14-1.39
Combined vs. pharmacotherapy	46	**1.27**	1.12-1.43	58	39-69	**0.02**	**1.25**	1.14-1.37
Combined vs. psychotherapy + placebo	10	1.19	0.95-1.52	39	0-69	**0.02**	**1.30**	1.06-1.59
Combined vs. placebo	4	1.15	0.73-1.79	60	0-84	0.39	**1.47**	1.20-1.75
Psychotherapy vs. pharmacotherapy	59	0.98	0.91-1.06	41	16-57	0.38	0.99	0.92-1.08
Psychotherapy vs. psychotherapy + placebo	2	0.88	0.60-1.30	16	NA	NA	1.03	0.84-1.27
Psychotherapy vs. placebo	8	1.20	0.93-1.59	46	0-74	0.67	1.16	0.98-1.39
Pharmacotherapy vs. psychotherapy + placebo	6	1.05	0.76-1.45	53	0-79	0.45	1.04	0.85-1.27
Pharmacotherapy vs. placebo	12	**1.25**	1.09-1.45	0	0-50	0.68	1.18	0.99-1.39
Psychotherapy + placebo vs. placebo	4	1.00	0.76-1.30	0	0-68	0.29	0.88	0.69-1.12
Remission								
Combined vs. psychotherapy	15	**1.20**	1.02-1.41	25	0-59	0.76	**1.22**	1.08-1.39
Combined vs. pharmacotherapy	25	**1.28**	1.10-1.52	57	27-72	0.22	**1.23**	1.09-1.39
Combined vs. psychotherapy + placebo	6	1.18	0.71-1.92	67	0-84	0.79	1.09	0.82-1.45
Combined vs. placebo	2	**1.52**	1.02-2.22	0	NA	NA	**1.59**	1.27-2.00
Psychotherapy vs. pharmacotherapy	47	1.01	0.93-1.10	29	0-50	0.90	1.01	0.93-1.10
Psychotherapy vs. psychotherapy + placebo	1	0.66	0.40-1.05	NA	NA	NA	0.89	0.67-1.19
Psychotherapy vs. placebo	7	**1.37**	1.05-1.79	41	0-74	**0.03**	**1.30**	1.05-1.59
Pharmacotherapy vs. psychotherapy + placebo	4	0.81	0.32-2.04	84	47-92	0.42	0.89	0.67-1.19
Pharmacotherapy vs. placebo	9	**1.33**	1.10-1.64	22	0-64	**0.04**	**1.28**	1.05-1.59
Psychotherapy + placebo vs. placebo	2	1.25	0.76-2.04	0	NA	NA	0.69	0.49-0.96
Acceptability								
Combined vs. psychotherapy	18	1.08	0.92-1.28	0	0-44	0.99	1.06	0.89-1.26
Combined vs. pharmacotherapy	41	**1.29**	1.13-1.47	0	0-33	0.74	**1.23**	1.05-1.45
Combined vs. psychotherapy + placebo	9	0.96	0.59-1.58	18	0-62	0.50	0.98	0.66-1.46
Combined vs. placebo	4	1.35	0.56-3.27	24	0-75	0.12	1.25	0.94-1.66
Psychotherapy vs. pharmacotherapy	58	**1.16**	1.02-1.31	28	0-48	0.04	**1.17**	1.02-1.32
Psychotherapy vs. psychotherapy + placebo	2	0.54	0.13-2.36	36	NA	NA	0.93	0.62-1.38
Psychotherapy vs. placebo	8	1.34	0.86-2.09	62	0-81	0.15	1.18	0.91-1.53
Pharmacotherapy vs. psychotherapy + placebo	7	0.72	0.43-1.21	27	0-69	0.67	0.77	0.50-1.19
Pharmacotherapy vs. placebo	12	0.98	0.72-1.33	40	0-68	0.38	1.02	0.79-1.30
Psychotherapy + placebo vs. placebo	4	1.06	0.57-1.95	0	0-68	0.31	0.79	0.51-1.21
Standardized mean difference (SMD)	**N**	**SMD**	**95% CI**	**I^2**	**95% CI**	**Egger**	**SMD**	**95% CI**
Combined vs. psychotherapy	19	0.15	–0.05 to 0.35	69	45-79	0.05	**0.30**	0.14-0.45
Combined vs. pharmacotherapy	41	**0.37**	0.23-0.53	68	54-76	**0.03**	**0.33**	0.20-0.47
Combined vs. psychotherapy + placebo	7	0.07	–0.20 to 0.34	12	0-63	0.61	0.16	–0.18 to 0.49
Combined vs. placebo	2	0.08	–0.40 to 0.55	0	NA	NA	**0.43**	0.10-0.76
Psychotherapy vs. pharmacotherapy	50	0.00	–0.13 to 0.12	68	55-75	**0.03**	0.04	–0.09 to 0.16
Psychotherapy vs. psychotherapy + placebo	2	–0.19	–0.57 to 0.18	0	NA	NA	–0.14	–0.49 to 0.21
Psychotherapy vs. placebo	4	0.19	–0.37 to 0.75	82	34-91	0.89	0.13	–0.19 to 0.45

Table 3 Results of pairwise and network meta-analyses (*continued*)

	Pairwise meta-analyses						Network meta-analysis	
	N	RR	95% CI	I^2	95% CI	Egger	RR	95% CI
Pharmacotherapy vs. psychotherapy + placebo	4	–0.24	–0.58 to 0.10	16	0-73	0.76	–0.18	–0.52 to 0.16
Pharmacotherapy vs. placebo	6	0.19	–0.13 to 0.50	48	0-77	0.84	0.10	–0.22 to 0.41
Psychotherapy + placebo vs. placebo	2	–0.11	–0.59 to 0.38	0	NA	NA	–0.27	–0.71 to 0.16

RR – relative risk, NA – not available
Significant results are highlighted in bold prints

psychotherapy and pharmacotherapy), only one predictor was found to be significant ("other" pharmacotherapy versus SSRI: coefficient=–0.55, SE=0.22, p=0.01).

Long-term effects

We calculated response rates for studies reporting follow-up outcomes at 6 to 12 months. The pairwise meta-analyses indicated that combined treatment was more effective than pharmacotherapy at 6 to 12 months follow-up (RR=0.71, 95% CI: 0.60-0.84). The other two comparisons did not indicate a significant difference. The network meta-analysis, however, indicated that combined treatment was not only more effective than pharmacotherapy (RR=0.72, 95% CI: 0.62-0.83) but also than psychotherapy (RR=0.84, 95% CI: 0.71-0.99), and that psychotherapy was more effective than pharmacotherapy (RR=0.85, 95% CI: 0.74-0.98).

The design-by-treatment interaction model did not indicate global inconsistency in the network (X^2=0.12, df=3, p for the null hypothesis of consistency in the network: 0.99). Because the time to follow-up varied between 6 and 12 months, we conducted a meta-regression analysis to examine whether time to follow-up was associated with the outcome, but this association was not found (all p values >0.32).

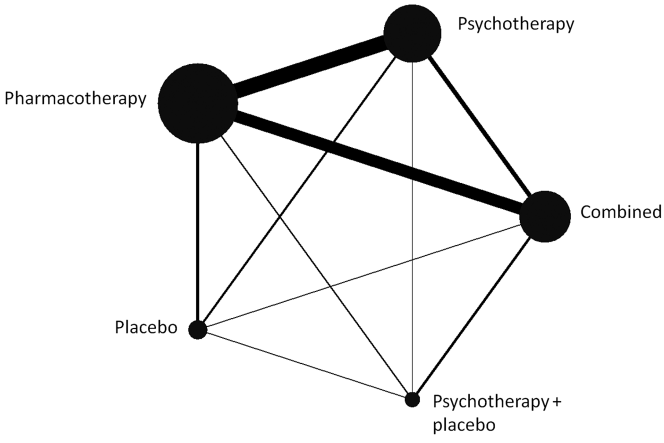

Figure 2 Network plot for response to psychotherapy, pharmacotherapy, combination of psychotherapy and pharmacotherapy, combination of psychotherapy and placebo, and placebo only in depression. The nodes and edges are weighted according to the number of participants and comparisons.

DISCUSSION

In this network meta-analysis, we assessed comparative data from 101 randomized trials and found that combination treatment was more effective than psychotherapy or pharmacotherapy alone in the treatment of adult depression, and that there were no significant differences between psychotherapy and pharmacotherapy.

We also found that acceptability, defined on the basis of study drop-out for any reason, was higher in combined treatment than in pharmacotherapy alone, and in psychotherapy than in pharmacotherapy. Acceptability of antidepressants may be lower due to side effects or because many patients prefer psychotherapy over pharmacotherapy[134]. Combined treatment may therefore be the best option for the treatment of depression both in terms of efficacy and acceptability and, from the perspective of acceptability, pharmacotherapy alone may be not optimal.

The majority of studies were aimed at patient populations with moderate depression. However, this must be considered with caution. We used the average depression scores per study, meaning that within each study the severity of depression could still range from mild to severe. In the relatively few studies on severe depression, we also found that combined treatment was more effective than pharmacotherapy. Unfortunately, only two studies examined combined treatment versus psychotherapy alone among patients with severe depression, so we cannot be certain whether combined treatment is superior for these people. Individual patient data meta-analyses have suggested that baseline depression severity does not moderate the efficacy of CBT versus antidepressant treatment[135], or CBT over pill placebo[136]. This supports the notion that combined treatment should be the first option for moderate and probably also severe depression. Unfortunately, there were too few studies in patients with mild depressive disorders to say anything about the relative effects of combined treatment, psychotherapy and pharmacotherapy.

There is evidence suggesting that a significant proportion of patients with depression receive psychotropic medication without psychotherapy[137,138]. The results of our meta-analysis suggests that this is probably not the optimal option in terms of

Table 4 Results of sensitivity analyses (all with response as outcome)

	Pairwise meta-analyses						Network meta-analysis		
	N	RR	95% CI	I^2	95% CI	Egger	RR	95% CI	χ^2 (df), p
Optimized pharmacotherapy									
Combined vs. psychotherapy	15	**1.27**	1.08-1.49	53	0-73	0.38	**1.20**	1.08-1.35	1.20 (3), 0.75
Combined vs. pharmacotherapy	25	**1.16**	1.02-1.33	52	15-68	0.91	**1.19**	1.06-1.33	
Psychotherapy vs. pharmacotherapy	45	0.99	0.91-1.08	44	14-60	0.75	0.99	0.91-1.08	
Optimized psychotherapy									
Combined vs. psychotherapy	9	**1.33**	1.18-1.52	14	0-60	0.42	**1.25**	1.08-1.47	0.47 (3), 0.93
Combined vs. pharmacotherapy	19	**1.27**	1.06-1.49	72	53-81	0.33	**1.27**	1.10-1.45	
Psychotherapy vs. pharmacotherapy	30	1.00	0.90-1.11	49	15-66	0.44	1.00	0.89-1.12	
Low risk of bias (self-report rated as low risk)									
Combined vs. psychotherapy	6	1.33	0.98-1.79	49	0-78	0.24	**1.45**	1.16-1.82	1.06 (3), 0.79
Combined vs. pharmacotherapy	17	**1.32**	1.02-1.67	70	45-80	0.88	**1.27**	1.05-1.54	
Psychotherapy vs. pharmacotherapy	16	0.87	0.76-0.99	41	0-66	0.08	0.87	0.74-1.03	
Low risk of bias (self-report rated as high risk)									
Combined vs. psychotherapy	5	**1.52**	1.32-1.75	0	0-64	0.59	**1.43**	1.15-1.79	0.02 (3), 1.00
Combined vs. pharmacotherapy	13	1.27	0.96-1.67	70	39-81	0.87	**1.23**	1.02-1.49	
Psychotherapy vs. pharmacotherapy	14	0.88	0.79-1.00	30	0-62	**0.04**	0.86	0.74-1.01	
Placebo controlled excluded									
Combined vs. psychotherapy	16	**1.28**	1.10-1.49	50	0-70	0.56	**1.32**	1.18-1.47	0.66 (3), 0.88
Combined vs. pharmacotherapy	39	**1.30**	1.15-1.47	58	37-70	**0.02**	**1.27**	1.15-1.41	
Psychotherapy vs. pharmacotherapy	48	0.94	0.87-1.03	40	10-57	0.68	0.96	0.88-1.05	
One effect size per study									
Combined vs. psychotherapy	19	**1.25**	1.09-1.43	46	0-67	0.40	**1.25**	1.12-1.39	0.27 (3), 0.97
Combined vs. pharmacotherapy	43	**1.27**	1.12-1.43	61	43-71	**0.02**	**1.25**	1.14-1.37	
Psychotherapy vs. pharmacotherapy	50	0.99	0.90-1.08	50	26-63	0.45	1.00	0.92-1.09	

RR – relative risk
Significant results are highlighted in bold prints

quality of care. Although the effects of psychotherapy and pharmacotherapy are comparable and individual patients may have different clinical situations and specific preferences, psychotherapy is on average more acceptable than pharmacotherapy alone. Findings from this paper clearly show that combined treatment is the best option in moderate depression, and in routine clinical care it would be better to consider psychotherapy as the first choice when only one treatment is offered to a patient. The National Health Service in the UK and other health care systems in the world, including low and middle income countries[139], should model themselves accordingly and invest more resources in non-pharmacological interventions for depression.

In real-world settings, pharmacotherapy and psychotherapy are typically provided by different clinicians and sometimes even at different clinics, with antidepressant medication often being prescribed in primary care and psychotherapy delivered in secondary care or settings outside of the hospital. Moreover, funding of services varies across countries, with different structures for medication and psychotherapy. This may complicate the use of combined treatments. From this perspective, collaborative care offers good opportunities for the dissemination of combined treatments[140].

In the majority of trials included in this meta-analysis, psychotherapy was delivered in an individual format. Only a limited number of trials examined group psychotherapies, and none of the trials used guided self-help or Internet-based psychotherapies. It is known from other research that psychotherapies can effectively be delivered in several different formats, including in groups, by telephone, through guided self-help, and via the Internet[141,142]. There are no indications that treatment format is associated with different effects of psychotherapy, as long as at least some personal support is given by a professional. It would

Table 5 Results of analyses focusing on chronic/treatment-resistant and mild/moderate/severe depression (all with response as outcome)

	Pairwise meta-analyses						Network meta-analyses		
	N	RR	95% CI	I^2	95% CI	Egger	RR	95% CI	χ^2 (df), p
Chronic or treatment-resistant depression									
Combined vs. psychotherapy	3	**1.45**	1.16-1.79	55	0-86	1.00	**1.59**	1.23-2.04	2.47 (2), 0.29
Combined vs. pharmacotherapy	10	**1.41**	1.12-1.75	73	41-84	0.37	**1.39**	1.15-1.67	
Psychotherapy vs. pharmacotherapy	6	0.84	0.70-1.00	25	0-70	0.37	0.87	0.68-1.10	
Severe depression									
Combined vs. psychotherapy	2	1.35	0.85-2.17	65	NA	NA	1.33	0.91-1.92	0.66 (3), 0.88
Combined vs. pharmacotherapy	6	**1.45**	1.14-1.82	35	0-73	0.80	**1.45**	1.10-1.89	
Psychotherapy vs. pharmacotherapy	4	1.18	0.70-1.96	54	0-83	0.33	1.09	0.72-1.64	
Moderate depression									
Combined vs. psychotherapy	11	1.14	0.99-1.30	0	0-51	0.30	**1.19**	1.05-1.37	0.48(30), 0.92
Combined vs. pharmacotherapy	18	**1.28**	1.10-1.47	34	0-62	0.03	**1.23**	1.09-1.41	
Psychotherapy vs. pharmacotherapy	32	1.02	0.93-1.12	23	0-50	0.35	1.03	0.94-1.14	
Mild depression									
Combined vs. psychotherapy	1	1.39	0.65-2.94	0	NA	NA	0.97	0.52-1.82	0.89(1), 0.35
Combined vs. pharmacotherapy	1	0.85	0.56-1.30	0	NA	NA	1.04	0.57-1.89	
Psychotherapy vs. pharmacotherapy	5	1.14	0.77-1.69	52	0-81	0.79	1.08	0.75-1.54	

RR – relative risk, NA – not available
Significant results are highlighted in bold prints

be useful to further explore such different therapy formats in combined treatment, because these formats require less resources and are often easier to implement than intensive individual therapies. This could potentially facilitate the use of combined treatments in routine care.

We also found that combined treatment was superior to psychotherapy and pharmacotherapy alone in chronic or treatment-resistant depression. That should be considered with caution, because we pooled all studies of chronic and treatment-resistant depression into one group, and may have missed specific outcomes for the two conditions. However, this finding is important from a clinical perspective and suggests that combined treatment should be preferred also in this problematic group.

It should be noted that there was some variability among the included studies in terms of the quality of pharmacotherapy administered, the quality of psychotherapy delivered and/or the quality of the study design and conduct. However, all sensitivity analyses limiting to trials of optimized pharmacotherapy, optimized psychotherapy or at low risk of bias produced very similar results. We therefore believe that our conclusions about the relative values of the three treatments are robust.

Unfortunately, the long-term effects of the treatments are still unknown. We calculated response rates for studies reporting follow-up outcomes at 6 months or longer. The only three studies reporting outcome data at more than 12 months were excluded from the analyses. The remaining studies were still heterogeneous in terms of continuation of treatment: in most studies no psychotherapy was given during follow-up, whereas pharmacotherapy was continued during the whole follow-up period in some studies, and tapered at some point during follow-up in some others. Other studies were completely naturalistic. We did find indications that, at 6 to 12 months after treatment start, combined treatment is more effective than psychotherapy or pharmacotherapy alone, and that psychotherapy is more effective than pharmacotherapy. However, these findings should be regarded as preliminary, because the studies varied widely in terms of what happened during follow-up. The finding that psychotherapy may be more effective than pharmacotherapy in the longer term is in line with previous meta-analytic research[143], and it has also been established previously that combined treatment may be more effective than pharmacotherapy alone[14]. The results of the analyses should, however, be considered with caution. Further research is clearly very much needed on the long-term effects of treatments for depression.

Very few studies have compared the effects of combined treatment with placebo. That is unfortunate, because a comparison with placebo would allow to better estimate the actual effects of combined treatment. Previous meta-analytic research suggested that the effects of combined treatment in depression and anxiety are the sum of the effects of psychotherapy and those of pharmacotherapy[11]. These findings were very preliminary, because of the broad CIs around the effect sizes found. However, they do suggest that the effects of psychotherapy and pharmacotherapy may be independent of each other, and can be applied separate-

ly. Unfortunately, the present meta-analysis did not find enough studies to confirm or falsify this finding.

We also found only a limited number of studies comparing the combination of psychotherapy and pharmacotherapy with the combination of psychotherapy and placebo. This comparison allows to examine the contribution of medication to the effects of combined treatment. A previous pairwise meta-analysis suggested that the medication contributed to the effects of combined treatment with a small effect size[144]. On the other hand, a comparison of psychotherapy plus placebo with psychotherapy alone would allow to estimate the impact of psychotherapy in addition to placebo effects.

This study has several strengths, but also some limitations. The number of trials was too small in specific subsamples, for example in severe or mild depression. Moreover, the majority of trials had at least one domain at high risk of bias. Finally, previous research has indicated that there may be some differences in efficacy and acceptability among specific types of medications[6]. In our network meta-analysis, we merged all antidepressants in one node, as we did not have enough studies across different medications to examine that in sufficient detail.

In conclusion, combined treatment is more effective than psychotherapy or pharmacotherapy alone in the short-term treatment of moderate depression, and there are no significant differences between psychotherapy and pharmacotherapy. This is also true in chronic and treatment-resistant depression, and probably also in severe depression. Acceptability is significantly better in combined treatment and psychotherapy, compared with pharmacotherapy. These findings suggest that guidelines should recommend combined treatment as the first option in the treatment of depression and, because of the higher acceptability, may recommend psychotherapy before pharmacotherapy, depending on the preferences of patients.

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Beyond depression: the expanding role of inflammation in psychiatric disorders

That inflammation plays an important role in depression has garnered considerable attention. Nevertheless, increasing data suggest that inflammation's effects on the brain may have broad relevance to our field, contributing to symptom presentations in many psychiatric disorders beyond depression.

The link between inflammation and depression is undeniable[1]. Patients with major depression reliably exhibit increases in immune molecules that are typically associated with chronic inflammation, including inflammatory cytokines – such as tumor necrosis factor, interleukin (IL)-1 beta and IL-6 – and acute phase proteins, such as C-reactive protein (CRP)[2].

Increased inflammatory responses also exist in post-mortem brain samples of depressed individuals, with activation of inflammatory signaling pathways in brain parenchyma, trafficking of immune cells to the brain, and activation of microglia[2].

In addition, administration of inflammatory cytokines such as interferon (IFN)-alpha, or inflammatory stimuli, including typhoid vaccination and endotoxin, induce depressive symptoms. Inflammatory markers, including IL-6 and CRP, predict the development of depressive disorders[2]. Finally, blockade of inflammatory cytokines has been shown to reduce depressive symptoms, especially in patients with autoimmune and inflammatory disorders[3,4].

Although these findings support an impressive argument for a special link between inflammation and depression, increased inflammation only occurs in a subset of depressed patients, being present in 25-50% of them, depending on the sample[4,5]. Factors that contribute to increased inflammation in depression include stress, especially early life stress, metabolic factors such as obesity and metabolic syndrome, medical illnesses and their treatments, and treatment resistance[2,6]. So, at best, inflamed depressed subjects represent a depressive subtype.

Increased inflammation also exists in multiple other psychiatric disorders, including bipolar disorder, anxiety disorders, post-traumatic stress disorder (PTSD) and schizophrenia[2,7]. Thus, inflammation is agnostic to diagnosis. Indeed, when significant inflammation is present, its effects on neurotransmitters and neurocircuits contribute to specific symptom profiles that are relevant to multiple psychiatric disorders[2].

A rich body of data has documented the effects of inflammation on the brain[1,2]. Inflammatory cytokines and their downstream signaling pathways reduce monoamine availability, by decreasing the synthesis and release and increasing the reuptake of serotonin, norepinephrine and dopamine. Through effects on astrocytes and microglia, inflammatory cytokines increase the release and decrease the reuptake of glutamate, contributing to a spillover of excess glutamate outside the synapse that can bind to extrasynaptic glutamate receptors, which can lead to excitotoxicity[2].

Inflammatory cytokines also activate the kynurenine pathway, which generates neuroactive metabolites, including kynurenic acid and quinolinic acid, while also decreasing the production of growth factors, such as brain derived neurotrophic factor, contributing to a disruption of neurogenesis and ultimately synaptic plasticity[1,2].

Given that conventional antidepressants act by increasing monoamine availability, have no effects on glutamate metabolism and in part depend on neurogenesis for their efficacy, it is not surprising that inflammation is associated with treatment resistance and predicts response to alternative treatment strategies such as ketamine and electroconvulsive therapy.

The effects of inflammation on neurotransmitter systems ultimately affect neurocircuitry. Neuroimaging studies indicate that neurocircuits regulating motivation and motor activity, as well as arousal, anxiety and alarm, are reliably affected[2]. Administration of inflammatory stimuli – including IFN-alpha, typhoid vaccination and endotoxin – all reduce activity in reward-related regions of the brain, such as the ventral striatum and nucleus accumbens, an effect that is linked to decreased dopamine metabolism as well as increased basal ganglia glutamate, and is accompanied by a decreased willingness to expend effort for reward, while sensitivity to reward remains intact[2,6].

Of special relevance to psychiatric patients, endogenous inflammation as reflected by increased CRP is associated with both decreased motivation (a key component of anhedonia) and psychomotor retardation, in association with decreased functional connectivity of the ventral and dorsal striatum with the ventromedial prefrontal cortex[8]. Although less well established, data indicate that administration of inflammatory stimuli also increases the sensitivity of key brain regions involved in the assessment and response to threat, including the dorsal anterior cingulate cortex, insula, hippocampus and amygdala[7]. In addition, endogenous increases in inflammation, as reflected by CRP, correlate with decreased functional connectivity between prefrontal cortex and the amygdala, in association with symptoms of anxiety in psychiatric patients.

Of note, the effects of inflammation on these specific neurocircuits may have derived from evolutionary imperatives to promote survival in sick or wounded animals, by conserving energy resources for the immunometabolic demands of fighting infection and wound healing through behavioral withdrawal (decreased motivation and motor activity), while protecting such vulnerable animals against future attack (arousal, anxiety and alarm)[2]. Supporting this notion is the emerging understanding of the relationship between immunometabolism and cognitive processes that shape decision-making and behavioral priorities in the context of inflammation[6].

Embracing the apparent transdiagnostic relevance of increased inflammation across psychiatric disorders raises the intriguing possibility that treatments targeting inflammation and its downstream effects on the brain may have widespread applicability. Moreover, given that patients with increased inflamma-

tion can be readily identified by inflammatory biomarkers, including CRP, we are uniquely poised to target inflammation-relevant symptom clusters, notably anhedonia and possibly anxiety, across psychiatric disorders. Such strategies represent an important step toward precision medicine in psychiatry.

Nevertheless, there are limitations. If the expectation is to treat disorders as they are defined by current nomenclature, therapies targeting inflammation and its effects on the brain may fall short. For example, a recent study found that an anti-cytokine therapy to block inflammation improved symptoms of anhedonia but did not separate from placebo on overall depression scores[9]. These results suggest that, in order to fully leverage current knowledge, clinical trials and clinical practice should take into consideration both the level of inflammation and relevant symptom profiles, treating the behavioral consequences of inflammation and not the disorder; whether it is anhedonia in PTSD, symptoms of amotivation in schizophrenia, or anxiety in depression.

While at first glance this approach may run counter to current clinical practice that focuses on diagnostic entities, recognizing that different symptom profiles within diagnoses may be driven by distinct pathophysiologic processes such as inflammation can be liberating. In addition, it may encourage the field to move away from the notion of one size fits all, to a multimodal approach that addresses the many contributing factors that drive the disorders we treat.

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Inflammation affects social experience: implications for mental health

Deemed as one of the breakthrough findings of the last two decades, inflammation – the immune system's first line of defense against foreign agents – can play a role in negative mental health states such as depression. For instance, depressed individuals have higher levels of circulating pro-inflammatory markers, and experimentally increasing inflammation in healthy subjects can induce depressed mood[1].

Part of the reason why inflammation can elicit depressive symptoms is that inflammatory processes can signal the brain to initiate "sickness behavior", an adaptive response to illness which includes symptoms such as loss of appetite, fatigue and social withdrawal, bearing a striking resemblance to the hallmark features of depression.

But, is inflammatory-induced depression simply a function of the lethargy that accompanies sickness, or does inflammation actually play a distinct and larger role in the psychological and socioemotional changes that often accompany depression? Mounting evidence shows that inflammation plays a role not only in sickness behavior, but also in enhancing feelings of social disconnection and in altering sensitivity to the social world. Investigating how inflammation affects social experience may be key to better understanding the many psychiatric disorders that involve altered social sensitivity.

To explore the causal effect of inflammation on social experience, researchers have used an inflammatory challenge paradigm, in which participants are randomly assigned to receive an injection of endotoxin, a bacterial agent that triggers a time-limited inflammatory response, or a placebo injection.

In the first study to examine the socioemotional consequences of this inflammatory challenge in humans, participants exposed to endotoxin not only showed depressed mood, but also an increase in feelings of social disconnection. Moreover, enhanced feelings of social disconnection mediated the relationship between inflammation and depressed mood[1]. A subsequent study with a larger sample replicated this basic finding, and also found that inflammatory-induced feelings of social disconnection were enhanced in female participants[2].

These findings demonstrate that inflammation is a powerful organizer of social experience. But why would this be? Though it may seem surprising that the activity of the immune system could affect social experience, this unlikely pairing may provide a survival advantage. Being in a "sick" state puts an organism in a uniquely vulnerable position, and thus sensitivity to the social world may be modulated in order to help survive this vulnerable situation. Thus, for humans as well as other social species, heightened inflammation may lead to: a) a greater sensitivity to threatening social experiences in order to avoid threats to well-being during times of illness, and b) a greater sensitivity to and approach towards loved ones who could provide support and care during these times[3]. Research provides support for both of these hypothesized outcomes.

In line with the idea that inflammation increases sensitivity to negative social experience, participants who showed larger increases in inflammation in response to endotoxin also showed greater pain-related neural activity in response to social rejection[4]. Similarly, participants exposed to endotoxin (vs. placebo) showed greater pain- and threat-related neural activity in response to negative social feedback[5]. This increased sensitivity to

negative experiences appears to be specific to the social domain: participants exposed to endotoxin showed enhanced neural activity in response to threatening stimuli that were social in nature (e.g., angry faces), but not to threatening stimuli that were non-social (e.g., snakes)[6].

Inflammation also increases sensitivity to positive social stimuli. Participants exposed to endotoxin reported having a greater desire to be with their loved ones, and showed enhanced reward-related neural activity to viewing images of their loved ones[7]. Similarly, participants exposed to endotoxin showed greater reward-related neural activity in response to receiving positive feedback from others[5]. These results support the idea that, during states of sickness, it may be adaptive to show increased reward- and approach-related responding to loved ones or to friendly others who could provide help and support. This inflammation-enhanced sensitivity to positive stimuli also seems specific to the social domain, as inflammation actually reduces reward-related neural responding to positive stimuli that are non-social, such as money[8].

Interestingly, the relationship between heightened inflammation and increased sensitivity to social stimuli is reminiscent of what is observed in loneliness, another emerging mental health issue. Lonely individuals show elevated inflammation, an increased sensitivity to negative social experiences, and, just like participants exposed to endotoxin, greater reward-related neural activity in response to viewing images of close others[9].

Thus, loneliness and states of heightened inflammation share the same characteristic pattern of heightened sensitivity to the social world. Building on these overlaps, we are currently examining whether experiences of loneliness and the corresponding enhanced social sensitivity can be reduced through an over-the-counter non-steroidal anti-inflammatory drug.

Altogether, these findings advocate for a stronger consideration of the role of inflammation in psychiatric disorders that involve altered social sensitivity. For instance, while not all forms of depression are inflammatory in nature, it is possible that inflammatory-related depression could be distinguished from non-inflammatory depression by a characteristic increase in reward-related neural activity to close others. Distinguishing between these forms of depression might help to better inform treatment strategies (e.g., anti-inflammatory drugs vs. cognitive-behavioral therapy).

Moreover, these findings also suggest a stronger consideration of the mental health consequences of inflammatory diseases. Those who have chronic inflammatory disorders may be at a greater risk for enhanced social sensitivities, which may put them at a higher risk for loneliness and depression, and may increase the strain placed on their social relationships.

Appreciating the intimate links between the immune system and social behavior may provide a new perspective from which to understand and treat mental health issues.

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The synaptic pruning hypothesis of schizophrenia: promises and challenges

Schizophrenia is widely considered a neurodevelopmental disorder, as suggested by its typical onset in adolescence and young adulthood, neurocognitive and social impairments preceding onset, and neuropathologic alterations of aberrant cellular organization, decreased neuronal volume, and dendritic spine loss.

Recent genome-wide association studies in large samples have revealed 108 genetic loci significantly associated with the risk of the disorder. The strongest risk was repeatedly identified in the major histocompatibility complex, a region rich with immune system genes and complex linkage disequilibrium patterns. Later studies determined that part of the variance for risk arises from the complement component 4 (C4) gene[1].

The complement system is involved in both immunological and regenerative processes, which include dampening inflammatory activation, angiogenesis, apoptotic cell removal, wound healing, and stem cell mobilization. In the central nervous system, complement factors play a role in synaptic pruning that may involve phagocytosis of redundant (or ineffective) synapses as well as enhanced pro-inflammatory cytokine secretion by glial cells inducing neuronal damage and death[2].

Exposure to maternal complement protein during pregnancy may be a risk factor for the development of schizophrenia in offspring[3]. Sellgren et al[4] used a reprogrammed in vitro model of microglia-mediated synapse engulfment and demonstrated increased synapse elimination in schizophrenia patient-derived neural cultures and isolated synaptosomes. Some of this effect was accounted for by carriers of schizophrenia risk-associated variants within the C4 locus.

All of these observations fit nicely into an early model original-

ly suggested by I. Feinberg, who postulated aberrant peri-adolescent pruning of synapses (resulting in either too much or too little pruning) as underlying schizophrenia[5]. In a subsequent paper, we suggested that an exaggerated pruning of synapses during adolescence/young adulthood could explain the onset of the disorder at that age[6]. This view is indirectly supported by phosphorus magnetic resonance spectroscopy studies that showed greater neuropil contraction in first episode schizophrenia[7], which was associated with a gene-dosage effect of C4A and C4B copy numbers[8].

While these observations may help connect several previously murky "dots" in our understanding of the pathophysiology of schizophrenia, several caveats are worth considering. First, the pathophysiology of schizophrenia may not simply be related to synapse loss. Substantive evidence show that abnormalities in myelin, neurons, oligodendrocytes, astrocytes and endothelial cells may also be involved. Human post-mortem studies that demonstrated dendritic spine loss, a proxy measure of synaptic pruning, are primarily localized to the basilar dendrites in the deeper layers of cortex, but not the entire cortex. Second, complement cascade alterations may not be unique to schizophrenia, with recent observations suggesting similar pathophysiological mechanisms in Alzheimer's disease and bipolar disorder.

Third, genetic factors underlying C4 expression may be only one among several possible mechanisms underlying alterations in synaptic pruning. Environmental factors, including intrauterine infections, may lead to complement and inflammatory alterations via maternal immune activation. Sleep deprivation may lead to synapse elimination via microglial phagocytosis. Traumatic brain injury could result in immune and complement activation with loss of synapses. Other genetic factors besides complement component genes affect synaptic pruning, such as genes that code for gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors (all of which are implicated in risk for schizophrenia). Furthermore, OTX2, which is associated with risk for bipolar disorder, impacts timing of synapse elimination via peri-neuronal nets.

Fourth, while complement alterations may be a useful starting point in understanding the schizophrenia puzzle, we are far from developing actionable biomarkers. Peripheral alterations in complement proteins are inconsistently seen, and vary across illness phases. Further, peripheral complement proteins do not cross the intact blood-brain barrier, and are not a proxy for complement activity in the brain. However, activated complement factors may lead to blood-brain barrier dysfunction which may further affect the progression of disease. Thus, future studies also need to examine cerebrospinal fluid samples, across prodromal, early and chronic psychotic states.

Finally, innovative studies are needed to directly demonstrate increased pruning in schizophrenia. Recent observations using a unique ligand for synaptic vesicle glycoprotein-2 showed reduced binding in schizophrenia that is interpreted as reduced synapse density[9]. These findings are awaiting replication.

Thus, many paths may lead to the hypothesized excess of synaptic pruning, and complement abnormalities may be only one such path. Further, accelerated synaptic pruning may be only one of many mechanisms underlying what we call schizophrenia, may not be unique to this illness, and may not be central to this collection of disease entities. The etiopathology of schizophrenia and related disorders is best conquered piecemeal (i.e., by identifying pathophysiologically distinct transdiagnostic subtypes, given their daunting heterogeneity). While the synaptic pruning model may be a promising step in the right direction, there are miles to go before we rest in this pursuit, and many more promises to keep.

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Gut microbiota: a missing link in psychiatry

The gut microbiota consists of the collection of microbes within the intestine, previously considered of little influence from a mental health perspective, but now regarded as a "virtual organ" weighing up to 1.5 kg in the adult intestine and producing molecules of primary importance for brain function and psychological well-being[1].

There are more bacteria in the human intestine than there are human cells in the body, and we feed these bacteria, while in turn they play a fundamental role in maintaining our overall health. The large intestine functions like a fermenter producing a variety of molecules, including most common neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, the serotonin precursor tryptophan, and the short chain fatty acids butyrate, propionate and acetate[2].

There are a variety of mechanisms enabling the gut microbes to communicate with the brain. These include the vagus nerve, short chain fatty acids, tryptophan and cytokines[3]. Certain microbes can only act centrally when the vagus nerve is intact, and can no longer do so following vagotomy. Previously, tryptophan was viewed as entirely of dietary origin, while now it has been es-

tablished that it is also synthesized by Bifidobacteria and enters the bloodstream, becoming available for brain entry and subsequent serotonin synthesis.

The gut microbiota has been implicated in a wide variety of neurological and psychiatric disorders, including Parkinson's disease, multiple sclerosis, depression, anxiety disorders and autism[4]. Much of what we know regarding the importance of gut microbes for brain function has been derived from studying germ-free animals, which do not have a gut microbiota. Such animals have an altered central serotonergic system, decreased dendritic spines in various brain regions, lower levels of trophic factors, along with abnormal neuron formation from progenitor cells in the hippocampus, altered myelination patterns in prefrontal cortex, and a defective blood-brain barrier.

Until relatively recently, the importance of the gut-brain-microbiota axis as a fundamental component of the stress response has largely been ignored. O'Mahony et al[5] studied the gut microbiota in a maternal separation model of depression in rats. They reported an elevation in corticosterone in such animals, together with an increase in pro-inflammatory cytokines and a decrease in the diversity of gut microbes.

The fecal microbiota was then sequenced in a depression study[6]. Forty-six patients with depression and 30 healthy controls were recruited. High-throughput pyrosequencing showed increased faecal bacterial diversity in those currently depressed, but not in a group who had responded to treatment. This suggests that increased diversity is a state rather than trait marker for depression. Despite the extensive inter-individual variability, levels of several predominant genera differed between depressed patients and controls. The former had increased levels of Enterobacteriaceae and Alistipes, but reduced levels of Faecalibacterium.

In a study conducted at APC Microbiome Ireland, depressed patients had elevated cortisol output together with decreased faecal microbial richness. When rats were given a humanized microbiota from depressed patients, as opposed to healthy controls, they developed a depressive phenotype from both a behavioral and immune perspective[7].

Thus, there is increasing evidence that some psychiatric disorders such as depression may be associated with a gut dysbiosis, a microbial imbalance.

Several studies have investigated the microbiome composition in patients with bipolar disorder[8]. The first published study involved 115 patients and reported decreased levels of Faecalibacterium. This finding was replicated in an Austrian study of 32 patients. However, a Danish study of 113 patients with newly-diagnosed bipolar disorder compared to unaffected first-degree relatives and healthy individuals found no differences in Faecalibacterium, while Flavonifractor, a bacterial genus that may induce oxidative stress and inflammation, was associated with the disorder.

Interestingly, two recent clinical trials have demonstrated a beneficial effect of adjunctive psychobiotics in patients with bipolar disorder. One was an uncontrolled pilot study which reported cognitive improvements in 20 remitted individuals following three months consumption of nine different strains of Lactobacillus or Bifidobacterium. The second was a randomized controlled trial involving 66 patients who had recently been hospitalized for mania. After discharge, these patients were randomly assigned to receive 24 weeks of an adjunctive Lactobacillus/Bifidobacterium combination or placebo. Re-hospitalization rates were significantly lower in those individuals who were taking the psychobiotic. Thus, preliminary data support the view that probiotics of the Lactobacillus and Bifidobacterium genera hold therapeutic potential in bipolar disorder.

Unlike genes in human cells, we can readily change genes in our microbiota by altering diet. There is increasing evidence that a poor quality diet may bring about the altered microbiota observed in mood disorders. Narrowing of dietary diversity with reduced intake of essential nutrients can reduce the availability of substrates for specific microbial growth and this may contribute to the intestinal dysbiosis of depression and other psychiatric disorders.

Over recent decades, dietary patterns in the West and elsewhere have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. This "Westernization" of diets results in dysbiosis, which may at least partially contribute to the increasing incidence of chronic inflammatory disorders, such as depression. The Mediterranean diet is associated with lower rates of depression and impacts optimally on the gut microbiota. Preliminary evidence indicates that such a diet may have antidepressant effects.

Individuals with depression or vulnerability to depression should be encouraged to enhance a plant-based diet with a high content of grains and fibres[9]. A decreased consumption of red meat, especially of processed meat, and a regular intake of fish and fermented foods, is optimal from a mental health perspective. The intake of refined sugars should be restricted.

Incorporating the gut microbiota in our studies of stress-related psychiatric illnesses expands the range of therapeutic targets, not only for pharmacological interventions, but also for nutritional ones. This may be one of the missing links that have restricted therapeutic advances in psychiatry during the past decades.

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Transcriptome-wide association analysis offers novel opportunities for clinical translation of genetic discoveries on mental disorders

Large-scale genetic studies have identified hundreds of robust statistical associations between genetic variants and risk for mental disorders, including depression[1] and schizophrenia[2]. These findings provide clear evidence for a polygenic architecture of those disorders, i.e., disease risk is influenced by thousands of genetic variants with individually small effects.

Due to the polygenic nature of mental disorders, the actual gene mechanisms underlying the pathophysiological pathways remain largely unknown. A key challenge is to elucidate the downstream molecular consequences underlying the genetic associations. Here we illustrate the value of integrating genetics and transcriptomics (i.e., the study of the level and regulation of gene expression in human cells) and how this approach has improved our understanding of the biological mechanisms underlying psychiatric disease risk. We further discuss how this methodology may contribute to developing improved therapeutics for mental disorders.

Determining the downstream molecular consequences of genetic risk factors for psychiatric disease is challenging for two reasons. First, the majority of disease-associated genetic risk factors are located in non-coding regions of the genome, suggesting that these genetic variants act through the regulation of gene expression rather than by directly altering the protein product. Second, due to extensive linkage disequilibrium (LD) in the genome, genetic studies alone are unable to distinguish causal variants from correlated non-functional variants within an LD block. Indeed, the genetic variant may only be statistically correlated with disease risk and may therefore not provide useful information on the causal disease mechanisms. Therefore, it is important to extend genetic studies by integrating functionally relevant intermediate measures reflecting molecular disease mechanisms (i.e., gene expression).

To this end, Gamazon et al[3] have developed a novel method that integrates genetic and transcriptomic information. This approach, referred to as PrediXcan, is the first transcriptome-wide association study (TWAS) methodology and allows researchers to identify genes whose expression is significantly associated with disease risk. It utilizes genotype and gene expression data from a reference panel to determine the regulatory effects of genetic variants and to identify which genes are differentially expressed in patients compared to healthy controls. An example of a widely used reference panel is the GTEx resource[4], which links genotype data to gene expression levels in 48 tissues from 714 donors, including 13 brain regions from 216 donors.

TWAS methods, such as PrediXcan, have multiple advantages. First, use of genetically-determined gene expression from a psychiatrically healthy reference panel ensures that significant associations are not influenced by potential confounders. For example, disease-associated variables (such as the use of psychotropic drugs) may lead to differences in gene expression that are a consequence rather than a cause of psychiatric disease. Second, TWAS methods do not only identify differentially expressed genes between patients and controls, but also provide information on the direction of effect, by showing whether the expression of a gene is upregulated or downregulated in patients compared to controls. Third, the effect of a genetic variant on gene expression may be tissue-specific. TWAS allows researchers to investigate the tissue-specificity of genetic effects. For example, we have previously shown that the strongest enrichment of genetic effects on gene expression was observed in disease-relevant tissues (e.g., aortic artery for systolic blood pressure and hippocampus for Alzheimer's disease)[5].

We have recently integrated genetic and transcriptomic data for four mental disorders (schizophrenia, bipolar disorder, major depression and attention-deficit/hyperactivity disorder) to gain pathophysiological insights into the role of the brain, adrenal gland (neuroendocrine factors), and colon (gastrointestinal systems)[6]. We found novel genetic mechanisms underlying disease risk and identified putative causal genes. Interestingly, our analysis detected 70 genes that were not identified in the original genetic analyses, illustrating improved power of TWAS compared to genome wide association studies (GWAS). Our findings highlighted the importance of analyzing gene expression data collected in multiple tissues (beyond easily accessible whole blood samples), as 76% of the putative causal genes were detected only in difficult-to-acquire tissues such as the brain.

Integration of genetic and transcriptomic data will provide excellent opportunities to produce improved therapeutics for mental disorders. Genetic discoveries may accelerate drug repositioning by identifying genes that are targeted by existing pharmaceutical compounds, an approach known as drug repurposing[7,8]. The development of a new drug takes on average 13-15 years and costs $2.5-3.5 billion, with only a ~10% chance that a new therapy will be successfully approved by government regulatory agencies. In contrast, drug repurposing allows increased efficiency and lower costs, because candidates have already established safety profiles from Phase I clinical trials, with time to approval estimated at 6.5 years at an average cost of $350 million. Drugs that have been linked to disorders through genetic studies are reported to be twice as likely to be clinically approved compared to drugs with no such links[7].

TWAS adds value beyond genetics as it provides essential information on whether a drug is predicted to reverse patterns of gene expression in patients and may therefore be able to reverse the disease phenotype. For example, if a disease-associated gene shows downregulated levels of gene expression in patients, we might aim to identify a drug that increases the expression of that gene, while drugs that decrease the expression may not be beneficial or even worsen disease symptoms. So et al[9], using PrediXcan, identified a number of repurposing candidates, many of which were relevant to mental disorders. We expect that future studies exploring drugs with different mechanisms of action will

reveal drug candidates that are not yet prescribed for the treatment of psychiatric disease (e.g., immune response drugs).

In conclusion, large-scale genetic studies provide a wealth of information of direct clinical relevance. Integration with other types of -omics data will be essential to elucidating biological mechanisms, identification of novel drugs, and translation of findings into the clinic.

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Validating digital phenotyping technologies for clinical use: the critical importance of "resolution"

Digital phenotyping, defined as the *in situ* data collection of people's phenotypes using digital devices, is an increasingly attractive method for understanding and treating psychiatric disorders[1]. The popularity of this method reflects, in part, the near ubiquity of smartphones, geolocation, social media, and other behavioral and physiological recording technologies in many modern societies. These technologies are relatively inexpensive and often yield continuous data streams that can be collected unobtrusively while people navigate their daily routine. This has the benefit of extending the geographical boundaries of assessment well beyond the traditional clinical setting and can potentially improve the effectiveness and reduce the cost of various interventions.

To date there is an impressive literature demonstrating "proof of principle/concept" for a wide range of technologies[2]. The voluminous material typically yielded by these technologies lends nicely to "big data" and complex computational approaches to understanding them. Indeed, the literature is replete with algorithms showing impressive accuracies for predicting a slew of clinical events and conditions using these technologies. To our knowledge, however, none have been approved for clinical psychiatric or psychological use by a governmental regulatory agency, and few, if any, have been adopted by clinicians, patients or organizations. This is in stark contrast to medicine more generally, which has adopted a large number of ambulatory objective technologies for a growing number of assessment and treatment solutions[3].

We believe that the challenges in implementing these technologies reflect, in part, a lack of psychometrics to effectively evaluate and understand them[4]. Traditionally, measures of psychiatric/psychological phenomena are evaluated using reliability and validity. Reliability concerns the consistency of a measure across time (test-retest reliability), individual items of the measure (e.g., internal consistency), informants (e.g., inter-rater reliability), and situations (e.g., situational reliability). On the other hand, validity concerns the accuracy of the measure, evaluated based on putative structure (e.g., structural validity) and potential convergence with conceptually related (e.g., convergent measure) and unrelated (e.g., discriminant validity) constructs, and clinically relevant criteria (e.g., concurrent and predictive criterion validity).

Importantly, the reliability and validity of measures in clinical psychiatry are far below those acceptable in other sciences. Reliability values explaining 50% of score variance are generally considered acceptable[5]. Validity values are even more liberally interpreted: for example, measures showing less than 50% overlapping variance with conceptually relevant measures are often considered acceptable, if not good/excellent[2]. Such large amounts of unexplained variance would be unacceptable in many applied medicine, physics, chemistry, engineering, biological, computer, informatics and related sciences.

Why are reliability and validity insufficient for understanding psychiatric phenomena? Psychiatric phenotypes are not static across time and space. When measured using sufficiently "high resolution" optics we see that, for example, psychosis varies as a function of proximity to stressful situations, borderline symptoms primarily emerge as a function of proximity to interpersonal "objects", and substance use craving waxes and wanes in proximity to substance-related cues[2,6]. Even psychological constructs like narcissism and cognition vary considerably over temporal and spatial epochs using high resolution measures[6,7]. For example, "sundowning" effects, involving progressive deterioration of fluid cognitive resources throughout the day, are a signature of many neurodegenerative disorders and a potentially useful target for discriminating dementia from depression.

Currently used clinical measures offer limited information regarding the temporal and spatial dynamics underlying psychiatric phenotypes. Structured clinical interviews, personality tests, symptom inventories and functioning measures generally rely on self-report responses and collateral observations/information obtained cross-sectionally during a spatially "constrained" interaction (i.e., a clinical visit), and usually have imprecise instructions with respect to how specific facets of the construct change as a function of temporal and spatial features. Moreover, few, if any, oft-used clinical measures provide data that can be scaled over user-defined periods of time or over clearly-opera-

tionalized spatial contexts.

Imagine if, for example, a patient's psychosis could be understood using an interface similar to online geographic maps. One could "zoom out" (decrease the resolution) to observe psychosis symptoms over days, weeks and months, and could "zoom in" (increase the resolution) to observe whether psychosis systematically change as a function of time (e.g., worse in the evening) or spatial conditions (e.g., worse when interacting with certain peers). This sort of dynamic data and interface would provide unprecedented opportunities for understanding psychiatric disorders and for personalizing pharmacological, psychosocial and emergency interventions.

Just as the reliability and validity of biomedical measures of, for example, glucose or heart rate[3] are only reported and evaluated during specific and controlled circumstances, so too should the reliability and validity of digital phenotyping technologies be understood as a function of time and space. Digital phenotyping technologies are not "reliable and valid" *per se*, but rather can have reliability and validity under specific circumstances and for specific purposes. Reporting psychometric features with regard to relevant temporal and spatial characteristics can help guide implementation of digital phenotyping technologies, improve interpretation of their data, and potentially help optimize signal and reduce noise. Conceivably, this can improve reliability and validity parameters such that they approximate those of biomedical tests more generally.

To illustrate how resolution can improve digital phenotyping validation efforts, consider natural language processing technologies used to quantify psychosis. A cursory review of the literature reveals that "validity" has been established, in that modest convergence is documented between various computationally-derived semantic speech features and "gold-standard" clinical symptom ratings[8]. This approach to validation seems inappropriate when one considers the mismatch in resolution between these measures – with the former being derived from systematic analysis of brief language samples procured during a fairly-contrived clinical interaction or cognitive task, and the latter representing an ordinal rating assigned by a clinician based on an extended clinical interview[9]. These ratings reflect very different temporal and spatial characteristics, and hence, failures to find large convergence is unsurprising. While machine learning-based algorithms connecting digital phenotyping technologies and clinical ratings have shown impressive accuracy, they have generally also ignored the overt resolution mismatch between these variables and have not demonstrated generalizability to new samples, speaking tasks or clinical measures[2,9].

To our knowledge, resolution is not generally considered in digital phenotyping research. In order for digital phenotyping of psychiatric disorders to be considered on-par with that of biomedical disorders more generally, their psychometrics need to be similarly precise. This precision can be achieved through deliberate consideration of "resolution".

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Ensuring Quality in Psychological Support (WHO EQUIP): developing a competent global workforce

Globally, the vast majority of people with mental health conditions do not receive effective care. Among people living with depression, only 1 in 5 persons in high-income countries and 1 in 27 in lower-middle income countries receive minimally adequate treatment[1]. There is a dearth of health workers trained in mental health care, with only one trained provider per 10,000 people in most countries[2]. One key action to improve access to mental health care is to expand psychological and psychosocial support services delivered by diverse cadres across settings[3].

There is now good evidence that persons who are not specialists in mental health can effectively deliver psychological interventions, but they must be adequately trained and supervised[4]. Non-specialist providers include primary care workers, community workers, psychosocial workers, teachers, family members and peers. However, unlike licensed professionals for whom there are professional associations to assure standards, there are usually no systems or mechanisms in place that check whether non-specialist providers have sufficient training and supervision to achieve minimum competency to effectively and safely deliver interventions. This raises the question: how can governments and the general population be assured that non-specialists provide quality care?

One way to address this challenge is to establish competency-based training approaches and competency assessment measures that governments, non-governmental organizations and other institutions can use to benchmark skills for safe and effective care. Competency measures can be used to determine who is or is not competent as well as to tailor supervision and supplementary training to address gaps in skills. Having competency targets in mind can also inform training duration and content

that may need to vary across sites or cadres. Competency-based training approaches have already demonstrated success in diverse areas of health care in low resource settings, including surgery and obstetric care[5,6].

To facilitate competency-based training in psychosocial support, psychological treatments, and foundational helping skills, the World Health Organization (WHO) is developing the Ensuring Quality in Psychological Support (EQUIP) platform (https://www.who.int/mental_health/emergencies/equip/en/).

The EQUIP platform aligns with WHO's work on universal health coverage, that is establishing competency frameworks across fields of health care. EQUIP will be an online resource to help program managers and trainers utilize competency assessments to evaluate trainings and to feedback those competency results to support trainee development and modify curricula.

The full suite will comprise tutorials on implementing competency assessments, including how to achieve interrater reliability with global rating standards and how to use role plays to assess competency. It will include guidance for trainers on delivering competency-based training programs, and for implementation and adaptation of psychological interventions. In addition, the EQUIP platform will offer training modules on common factors that can be selected based on competency assessment outcomes. Common factors are general elements of psychosocial support and psychological care – such as communication skills, empathy, collaboration, and helper-client alliance – that are vital ingredients for any intervention to be effective[7].

Contents of the EQUIP platform have been informed by a theory of change workshop attended by mental health and psychosocial service stakeholders with different practice experiences from diverse global settings. The EQUIP team has reviewed manuals and training materials for interventions delivered by non-specialists with effectiveness demonstrated in randomized controlled trials. This has led to the identification of competencies for both common factors and specific classes of psychological interventions (e.g., cognitive, interpersonal, problem solving, behavioral and trauma-focused techniques).

EQUIP will encompass a competency evaluation tool, the Enhancing Assessment of Common Therapeutic Factors (ENACT), that has been developed for role-play based assessment of mental health and psychosocial support skills for non-specialist and specialist providers across cultures, context and types of interventions[8,9]. In addition, a suite of competency assessment tools based on ENACT is being developed and tested. Below we briefly outline who, how, where and when EQUIP can be used.

Who can use EQUIP? EQUIP is intended for trainers, supervisors and project managers implementing psychosocial support and psychological interventions.

How can EQUIP be used? EQUIP can be used to improve implementation plans, competency assessments of trainees, and training and supervision curricula in common factors to accompany manualized interventions. Competency assessments may also be used to aid selection of trainees and to guide institutional certification after achieving minimum skill targets.

Where can EQUIP be used? EQUIP will be an online platform of resources with offline formats.

When can EQUIP be used? To refine the platform and its materials, EQUIP is being developed using a human-centered design approach to enhance usability and engagement, and piloted in multiple countries. After piloting, materials will be available in English, Arabic and Spanish.

Ultimately, EQUIP is intended to be a resource that will undergo iterative transformation based on feedback from the global practitioner community. Addressing mental health and psychosocial needs requires radical growth in the global workforce to ensure safe and effective delivery of psychosocial support and evidence-based psychological interventions. The EQUIP platform will make competency-based training and assessment resources widely available and adaptable to the contexts and needs of local organizations and practitioners.

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Defining pathological social withdrawal: proposed diagnostic criteria for hikikomori

In the late 1990s, a severe and prolonged form of social withdrawal typically observed among adolescents and youth transitioning to adulthood entered the collective national consciousness in Japan. Called "hikikomori", it has shifted in recent years from being viewed as a typical Japanese problem to an issue that may have global health implications[1]. This shift has been driven by increasing evidence of hikikomori in epidemiologic studies, clinical case series and media reports from around the world[2].

As attention to hikikomori grows across cultures and countries, so does the importance of establishing a clear and consistent definition of the disorder. About a decade ago, preliminary diagnostic criteria[3] and a semi-structured diagnostic interview[4] were developed. Over the last decade, we and others in this emerging field of research have gained a wider breadth of experience in evaluating, treating and following up a series of individuals with hikikomori, as well as their family members, in Japan and beyond. This has led to an evolution in our biopsychosocial understanding of the disorder[4,5], and an acute awareness of the limitations of its earlier definitions. We believe it is time now to provide an updated proposal of diagnostic criteria for hikikomori, which is presented here.

Hikikomori is a form of pathological social withdrawal or social isolation whose essential feature is physical isolation in one's home. The person must meet the following criteria: a) marked social isolation in one's home; b) duration of continuous social isolation of at least 6 months; c) significant functional impairment or distress associated with the social isolation.

Individuals who occasionally leave their home (2-3 days/week), rarely leave their home (1 day/week or less), or rarely leave a single room may be characterized as mild, moderate or severe, respectively. Individuals who leave their home frequently (4 or more days/week), by definition, do not meet criteria for hikikomori. The estimated continuous duration of social withdrawal should be noted. Individuals with a duration of at least 3 (but not 6) months of social isolation should be classified as pre-hikikomori. The age at onset is typically during adolescence or early adulthood. However, onset after the third decade of life is not rare, and homemakers and elderly who meet the above criteria can also receive the diagnosis.

Four aspects of this revised definition of hikikomori bear emphasis. First, the behavior of staying confined to home – the physical aspect of withdrawing and remaining socially isolated – remains hikikomori's central and defining feature. However, the definition adds clarification as to what frequency of going outside home still qualifies as "marked social isolation in one's home". Second, the requirement for avoidance of social situations and relationships has been removed. In our interviews assessing individuals for hikikomori[5], they commonly report having few meaningful social relationships and little social interaction, but deny avoiding social interaction. Many clinicians often wonder about what distinguishes hikikomori from social anxiety disorder, and this lack of avoidance is one of the primary differences.

Third, distress or functional impairment should be carefully evaluated. While impairment in the individual's functioning is vital to hikikomori being a pathological condition, subjective distress may not be present. Our in-depth clinical interviews with people with hikikomori[4] have revealed that many actually feel content in their social withdrawal, particularly in the earlier phase of the condition. Patients frequently describe a sense of relief at being able to escape from the painful realities of life outside the boundaries of their home. However, as the duration of social withdrawal gets longer, most people with hikikomori begin endorsing distress, such as feelings of loneliness[4].

Fourth, we have removed other psychiatric disorders as an exclusion criterion for hikikomori. It is clear that this disorder tends to co-occur with other conditions[6,7]. In our view, the frequency of co-occurring conditions increases the importance of addressing social withdrawal as a health issue. It is possible that hikikomori (pathological social withdrawal) co-occurs with a variety of psychiatric disorders as a contributor to psychopathology, similarly to how catatonia and panic attacks are now listed as specifiers to several mental disorder diagnoses.

With advances in digital and communication technologies that provide alternatives to in-person social interaction, hikikomori may become an increasingly relevant concern. We hope that these simplified diagnostic criteria may help standardize evaluation and encourage cross-cultural comparison of hikikomori.

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The revised German evidence- and consensus-based schizophrenia guideline

The German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) has just completed and published its revised national guideline on schizophrenia[1].

This guideline is evidence- and consensus-based according to the methodological criteria for clinical guidelines fulfilling the highest quality standard (S3) of the Standing Guideline Commis-

sion of the German Association of Scientific Medical Societies (AWMF)[2]. S3 standard is based on scientific evidence including systematic literature search and grading, evaluation and adaptation of available international high-quality guidelines, and a scientifically sound formal consensus by means of nominal group processes, structured consensus conferences and possible additional use of the Delphi technique[2].

For the revision process, the guideline was arranged into topic-specific modules, which were updated by members of the Steering, Expert and Consensus Groups of the Association. Thirty-eight stakeholders – including representatives from medical societies and other associations of the workforce from all fields involved in the diagnosis, treatment and care of schizophrenia, from patients' and relatives' advocacy groups, as well as more than 20 experts from different topic-related disciplines – were involved in the process.

Standardized operational procedures to deal with all potential financial and non-financial conflicts of interest were implemented. The guideline underwent several internal and external revision steps, including a public consultation phase, and was funded by the DGPPN without any public, ministerial or industry support. The guideline group produced a total of 162 recommendations and 8 statements. The document is freely available at the AWMF webpage (www.awmf.org), as a long (in German) and short (in German and English) version.

The guideline is structured in seven modules, covering all areas of diagnosis, treatment and management of schizophrenia. Module 1 describes the general principles of the management of schizophrenia, while module 2 focuses on differential diagnoses (including rare diseases such as autoimmune psychosis) and the detection of somatic comorbidities that may cause excess mortality. Module 3 describes the general aspects of treatment, focuses on developing course-specific treatment plans, and emphasizes the need for shared decision making.

Module 4 includes the available treatment interventions in schizophrenia. Submodule 4a covers all aspects of pharmacological and biological treatments, with a particular emphasis on side effect prevention and management. Submodule 4b focuses on psychotherapeutic and psychosocial interventions and family care. Submodule 4c gives recommendations for treatment under special clinical circumstances, such as comorbid mental illnesses (e.g., depression, post-traumatic stress disorder or obsessive-compulsive disorder), agitation and aggression, substance use disorders (tobacco, alcohol and cannabis), catatonia; childhood, adolescence and the elderly; pregnancy and breast feeding; as well as in people being at risk for psychosis. Submodule 4d covers issues of medical, social and occupational rehabilitation.

Module 5 refers to care coordination and is giving recommendations for an integrated cooperation of all service providers. Most importantly, the guideline group also produced recommendations for the necessary staffing of psychiatric hospital care to guarantee an optimal guideline-based treatment. Module 6 evaluates the cost-effectiveness of treatments, and Module 7 covers quality management in schizophrenia treatment and care.

The German guideline gives recommendations with different strengths (A: we recommend; B: we suggest; 0: it may be considered; KKP: good-clinical practice/expert recommendation), based on a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology[3].

Examples of particularly important recommendations are the following[1]: a) to offer regular monitoring of physical health to all persons with schizophrenia; b) to evaluate and classify symptoms suggesting typical medical comorbidities in every patient with schizophrenia; c) to offer magnetic resonance imaging to every person with a first-episode schizophrenia; d) to offer acute and maintenance antipsychotic drug treatment using the lowest possible dosage to every person with schizophrenia; e) to select an antipsychotic drug mainly based on the side effect profile; f) to work out the duration of maintenance treatment on an individual basis, offering the possibility for an early discontinuation (e.g., to reduce side effect burden), but also for a long-lasting treatment in every disease stage (to reduce the relapse likelihood); g) to offer clozapine monotherapy as soon as the criteria for treatment resistance are fulfilled, and antipsychotic drug combination treatment only if adequate response is not achieved with monotherapy with three different antipsychotics, including clozapine; h) to offer electroconvulsive treatment in cases of catatonia; i) to offer psychosocial interventions, exercise interventions and/or metformin (or topiramate) for weight gain; j) to offer cognitive behavioural therapy (CBT), psychoeducation and family interventions to every person with schizophrenia; k) to develop crisis plans and advance treatment arrangements to avoid compulsory admissions; l) to offer primarily CBT rather than antipsychotic drugs to persons at risk for developing psychosis, and m) to wait for two weeks before switching antipsychotic drugs in case of depressive symptoms, but also to offer an add-on antidepressant in case of a significant depressive syndrome. These examples highlight the scope of the guideline content, but should not be used in clinical practice without consulting the original text.

Compared to the guidelines of the UK National Institute for Health and Care Excellence (NICE)[4], the German guideline is putting more emphasis on specific challenging clinical situations and has involved a broad spectrum of stakeholders, which adds to its representativeness and acceptance.

We are planning to submit the currently available major schizophrenia guidelines, including our own, to a systematic quality check by using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument, as has been done with former guideline versions[5].

For the future, we believe that an international high-quality "core guideline", based on best available evidence and "neutral" international consensus, should be developed by the WPA and other international associations and stakeholders. This guideline should then be adapted to the special needs of national health care systems by the national psychiatric and other associations and stakeholders. This would have the potential to improve overall care for patients with schizophrenia, to harmonize treatment across countries and to reduce guideline developmental costs per country.

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Schizophrenia as parasitic behavior manipulation: can we put together the pieces of an evolutionary puzzle?

It is a disturbing fact that a diagnosis of schizophrenia is still associated with a poor prognosis concerning quality of life and community functioning, and that life expectancy of people with this diagnosis is reduced by about 14.5 years compared to the general population[1]. Over the last decades, this has changed very little, despite intensive research into drug development and psychological therapy. This calls for fresh ideas concerning the etiology of the disorder to pave the way for novel treatment approaches.

Even though it is undisputed that schizophrenia is highly heritable, decades of research have failed to find a conclusive answer concerning its genetic biology. One of the few replicated findings is that genes pertaining to immunological competency play a significant role, particularly those involved in the major histocompatibility complex[2]. It is also unclear why predisposing genes have remained in the genepool, despite their detrimental effect on reproduction, thus rendering schizophrenia an "evolutionary enigma"[3].

Accumulating evidence suggests that some cases of schizophrenia are associated with a latent infection with *Toxoplasma gondii*, a protozoic agent known to affect warm-blooded animals[4]. In essence, individuals with *T. gondii* antibodies have a 2.7-fold elevated risk for schizophrenia compared to unaffected subjects, and the risk for schizophrenia associated with the infection by far exceeds the risk conveyed by any single gene putatively involved in the etiology of the disorder[4]. In light of figures suggesting that about two billion people worldwide are infected with *T. gondii*, and observations that the risk of infection with this agent relies on the genetic make-up of one's major histocompatibility complex[2], there is a clear need for studying these associations in greater detail.

The reproductive cycle of *T. gondii* is complex, with felines being the definitive host for sexual reproduction. The felines' feces contain oocysts, which can infect intermediate hosts by oral pathways. There, asexually produced bradyzoites travel to the brain, the heart and other organs, where they build cysts and remain for the host's lifetime. The reproductive cycle of *T. gondii* closes when felines feed on infected animals through predation.

T. gondii has the potential to actively manipulate the intermediate host's behavior for its own reproductive benefit. Rodents infected with *T. gondii*, for example, display decreased vigilance for predators. Strikingly, infected rats lose their innate avoidance of cat urine odor. Instead, they seem to approach locations expressing cat (urine) odor in a "suicidal" manner, thus increasing their risk of predation.

Experimental evidence from rodent studies suggests that the parasite manipulates the host's dopamine turnover and impacts on glutamatergic neural pathways, which is entirely consistent with the prevailing neurotransmitter models of schizophrenia[5].

But what about the behavioral manifestations of *T. gondii* infection in human hosts? Might schizophrenia be seen as a possible phenotypic expression of the parasite's manipulation?

In fact, most researchers believe that human infection is an "accident" of *T. gondii* exposure[4]. From an evolutionary viewpoint, however, it is possible to argue that genetically vulnerable early humans (and their ancestors) were as logic a target to become an intermediate host as rodents now are. The manipulatory action of *T. gondii* in humans could have aimed at their exclusion from the social community, because in gregarious species like *Homo sapiens* individuals bare the greatest risk of predation when isolated from the social group[6].

Following this line of reasoning, many "core" symptoms associated with schizophrenia support the idea that the disorder may be the phenotypic correlate of manipulation by *T. gondii* ultimately promoting social exclusion. For example, social cognitive impairments lead patients to believe that others have malevolent intentions, thus giving way to paranoid ideation causing social withdrawal or aggression against the perceived perpetrator, which ultimately promotes marginalization of the individual. Negative symptoms such as affective flattening, apathy or abulia cause rejection from others, and many patients fail to experience social interaction as rewarding[7]. Together, it is possible to hypothesize that the typical signs and symptoms associated with schizophrenia may have served in the past the parasite's biological interests, i.e. to increase the risk of predation for its host by forcing the individual to leave or be expelled from his/her social community.

Current therapeutic approaches to schizophrenia mainly depend on the anti-dopaminergic action of antipsychotic drugs. Interestingly, some antipsychotics possess anti-parasitic properties, due to chemical similarities to naturally occurring plant

deterrents of parasites[4]. This invites speculations that drug efficacy in the treatment of schizophrenia might be related, in part, to the anti-parasitic effect of the medications. However, currently available drugs against *T. gondii* infection do not have the potential to ameliorate the symptoms of schizophrenia.

Parasitic behavior manipulation is widespread in nature, yet under-researched as a causative factor of disease in humans. This is so because knowledge about parasite-host interaction and other evolutionary aspects germane to medicine still linger to be implemented in curricula at medical schools[8]. Thus, both clinicians and pharmaceutical companies are oblivious to putative mechanisms of parasitic action.

However, if action were taken to follow up on the above evolutionary insights, one could see schizophrenia as an ancestral "vestige" from a time when early humans fell prey to large feline predators. Future research into schizophrenia may be advised to study the link between *T. gondii* infection, clinical symptomatology contributing to social exclusion, and genetic factors involving the major histocompatibility complex and other immunologically relevant genes such as DISC1[9], some of which have been positively selected during human evolution.

It might eventually turn out that there is a chance of causal treatment for schizophrenia realized by the development of new antibiotics against latent toxoplasmosis, rather than (or in addition to) reiterating attempts to ameliorate epiphenomena of the condition.

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Pneumonia may be more frequent and have more fatal outcomes with clozapine than with other second-generation antipsychotics

In 2005, the US Food and Drug Administration (FDA) requested a warning in the package insert of second-generation antipsychotics (SGAs), indicating that the use of those medications was associated with increased mortality in elderly people with behavioral disturbances. One of the causes of death mentioned in the FDA report was pneumonia.

Since then, evidence has progressively suggested that patients on clozapine are particularly prone to developing pneumonia. In Taiwan, Hung et al[1] found that clozapine was the only antipsychotic associated with a clear dose-dependent increase in the risk for recurrent pneumonia (adjusted risk ratio = 1.40), with patients re-exposed to the drug having a higher risk than those receiving it only prior to the baseline pneumonia. In a 25-month retrospective US study, pneumonia occurred in 34% of clozapine patients (odds ratio = 4.07 compared with the general population), whereas there was no significantly increased risk of pneumonia associated with the use of risperidone[2]. In a 12-year study in another US hospital, pneumonia was the top cause of medical admissions in clozapine patients (19% of cases)[3].

The increased risk of pneumonia from clozapine may be explained by swallowing disturbances common to all SGAs; clozapine's increased risk of sedation and hypersalivation; and clozapine's not-well-understood effects on the immune system[4].

Pneumonia during clozapine treatment may be particularly lethal. In a British drug discontinuation study, five deaths due to pneumonia were found in 529 clozapine patients, and none among 250 patients on long-acting risperidone[5]. In the Danish registry, Rodhe et al[6] explored myocarditis within 2 months of 3,262 clozapine initiations in outpatients. None of the 26 deaths was caused by myocarditis, while pneumonia caused 7 deaths (2.1 per 1,000 patients), making it by far the primary cause of death.

Since 2002, many cases of clozapine intoxication during pneumonia or other severe infections have been published. A systematic literature review through 2016 identified 40 cases[7]. Inflammation releases cytokines which inhibit the main metabolic enzyme of clozapine, CYP1A2, which increases clozapine levels. Clozapine has a narrow therapeutic range, and severe inflammation during pneumonia can cause clozapine intoxication, possibly leading to death by further increasing the risk of hypersalivation, sedation, aspiration, or even arrhythmia[4].

Here we provide new data obtained from VigiBase, the World Health Organization (WHO)'s global database, which receives spontaneously reported cases of suspected adverse drug reactions from 134 countries around the world, and currently includes nearly 20 million reports.

On April 9, 2019, we searched the WHO database for reports of pneumonia related to clozapine and three other SGAs, the most frequently used worldwide – risperidone, quetiapine and olanzapine. For clozapine we found 4,865 reports of pneumonia, which corresponds to 3.5% of all clozapine reports in the database and exceeds the 1,195 expected if clozapine had followed the general reporting in the database (0.9% of the reports relating to pneumonia). A standard statistical analysis for these data, combining statistical shrinkage and Bayesian confidence intervals for the observed-to-expected ratio, indicates a robust statistical association ($p<0.001$). Moreover, such association was observed in

separate analyses for all adult age groups and across the Americas, Asia, Europe and Oceania, reducing the likelihood of being due to report artifacts or case duplication. In contrast, there were fewer reports than expected in VigiBase for the other SGAs: 393 vs. 845 for risperidone, 622 vs. 650 for quetiapine, and 493 vs. 529 for olanzapine. More importantly, the number of pneumonia reports with fatal outcomes was dramatically higher for clozapine (1,577) than for the other SGAs (141, 105 and 147).

As the 1,577 fatal outcomes from pneumonia appeared very high, we compared this finding with other reported fatal outcomes associated with clozapine. The second reported fatal outcome was cardiac arrest, with 943 cases. Only 212 fatal outcomes were reported in 4,775 agranulocytosis cases. We found 144 fatal outcomes in 2,694 myocarditis reports.

Our analyses of the WHO database highlight pneumonia as a possible major cause of death in patients on clozapine, but alternative explanations for the observed reporting patterns must be considered. Risperidone, quetiapine and olanzapine are each prescribed much more frequently than clozapine worldwide, but the total number of reports in VigiBase is highest for clozapine. This may reflect the closer monitoring of patients on clozapine, although it cannot explain the higher proportion of reports on pneumonia, including associated fatal outcomes. On the other hand, clozapine is typically used in more treatment-refractory patients, who may be more severely ill, so it cannot be ruled out that these patients are at greater risk of developing or dying from pneumonia[4].

The literature clearly suggests long-term clozapine treatment to be less frequently associated with all-cause mortality than other antipsychotic use[8], but preventing deaths from pneumonia may further reduce mortality, since pneumonia may be killing many more clozapine patients than agranulocytosis or myocarditis, which are emphasized in the package insert. If other studies, particularly from the reliable Scandinavian registries, confirm and extend the Danish finding that pneumonia starts killing clozapine patients within the first 2 months of treatment, there may be a need to warn about pneumonia in the clozapine package insert.

Until then, two simple measures may help clinicians decrease the mortality risk in clozapine patients during pneumonia. First, patients and families should be told to call the psychiatrist if the patient develops a fever or any obvious sign of a severe infection. Second, if the patient has fever or an elevation in C-reactive protein, the clinician should pay attention to any sign of clozapine intoxication (including sedation, hypersalivation or myoclonus) and urgently measure trough (early morning before medication) clozapine levels to rule out clozapine intoxication. In the absence of rapid access to clozapine levels, the psychiatrist may consider halving the clozapine dose until the infection/inflammation has resolved.

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Early intervention in psychosis in low- and middle-income countries: a WPA initiative

Specialist early intervention in psychosis (EIP) services have been considered the "most positive development in mental health services since the beginning of community care"[1]. The development and implementation of specialist EIP services in high-income countries was predicated on the "critical period hypothesis", which argued that poor outcomes in psychosis accumulated in the first 2-5 years since onset of the disorder[2], and that longer duration of untreated psychosis (DUP) was associated with poorer outcomes[3].

Early intervention incorporates three different paradigms: assertive and high-quality evidence-based care by specialist teams in first-episode psychosis; early detection of untreated cases in the community (i.e., shortening of DUP); and interventions for young people at clinical high risk (CHR) – also known as ultra high risk (UHR) – for developing a psychotic disorder[4,5].

The most consistent evidence is from trials of specialist EIP care versus treatment as usual, which shows better short-to-medium clinical and functional outcomes for those receiving EIP care[6], as well as cost-effectiveness of EIP[7], while the evidence of specific effective CHR/UHR interventions to prevent the emergence of psychosis remains unclear[8,9].

Almost 80% of all patients with first-episode psychosis live in low- and middle-income countries (LMICs), where mental health services are scarce and most people do not get any form of mental health care[10]. Mental health treatment gap – the difference between those needing mental health care and those receiving it – is extraordinarily high in LMICs[11]. In the absence of adequate care, many people with psychotic disorders in LMICs end up restrained, neglected or simply abandoned.

Despite the burden of untreated or inadequately treated psychotic disorders, the resource scarcity in LMICs – inadequate funding, lack of basic services and shortage of trained professionals – means that it is not feasible to set up specialized EIP services when even basic care for mental disorders is lacking.

However, while "Western" models of care cannot be just translocated to LMICs, it should be possible to incorporate the principles and "therapeutic ingredients" of early intervention into routine mental health settings in LMICs, at all levels of care – primary (community), secondary and specialist tertiary (where these exist)[12,13].

To meet this challenge, the WPA has set up an Expert International Advisory Panel to develop a set of priorities, guidelines and recommendations for early intervention in LMIC settings. An initial meeting was held in May 2019 in Coventry, UK.

At this meeting, a small group of experts agreed on the needs and priorities that could guide the development of early intervention strategies in LMICs within the existing constraints of scarce resources.

The group reached consensus on several important points, as follows:

- Early intervention in LMICs needs a coordinated public health approach, with a comprehensive package of care provided free at the point of delivery.
- Early intervention principles can be meaningfully integrated into existing service structures in LMICs.
- LMIC communities are dynamic entities with strengths, assets and untapped potential, especially in the form of social capital stemming from interconnectedness, reciprocity and networks of care, which may offer innovative opportunities for integrating mental health care into existing help-seeking pathways.
- Such integration should occur in parallel with mental health awareness and anti-stigma campaigns.
- Pathways to mental health care in LMICs need to be carefully studied to identify "malleable" points where strategic public health interventions can help facilitate early access to care, thus reducing DUP.
- Services should cater for broadly identified psychosis (including mood disorders with psychotic symptoms) rather than narrowly defined schizophrenia.
- Interventions should be culturally adapted, appropriate, accessible and acceptable. The guiding principle should be that of effective interventions used whilst maintaining the dignity and the least restrictive way of working with service users.
- Some groups are particularly vulnerable, such as the homeless, young people without family support and migrant groups fleeing conflict, which deserve special focus.
- The WPA should leverage its reach and strengths to argue for greater funding into mental health care in LMICs with targeted campaigns for evidence-informed reform of care.

The group is planning a larger meeting in early 2020, where formal guidelines and recommendations will be agreed upon and adopted as part of the WPA initiative.

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The WPA Education, Science, Publication, and Research Initiative (ESPRI): jumpstarting scientific projects in low- and middle-income countries

The WPA's core mission is to promote the advancement of psychiatry and mental health all over the globe. Fostering an environment enabling state-of-the-art learning and research is an integral part of the WPA's toolbox to achieve that mission.

At the level of WPA Executive Committee, the Secretaries for Education, Scientific Publications and Scientific Sections closely collaborate to build and maintain that environment[1]. Hence, a new signature project of the WPA, the Education, Science, Publication, and Research Initiative (ESPRI), initially proposed and conceptualized by the Secretary for Scientific Sections and further developed and fully endorsed by all members of the Executive Committee, has now been launched as a joint initiative to stimulate groundbreaking education, publication and research projects in low- and middle-income countries (LMICs).

Results from the EMERALD project on emerging mental health systems in LMICs have alerted the global psychiatric community to the various challenges to sustainable mental health services, knowledge transfer and research[2,3]. But they have also highlighted how well-coordinated networks of stakeholders, capacity building activities, and dissemination can bring about change.

WPA's ESPRI is meant to stimulate the scientific aspects of these networks. Knowing that the low level of funding accorded to mental health in LMICs is a major impediment to putting promising ideas into practice, ESPRI aims at jumpstarting projects by providing seed funding to research groups.

These projects should ideally be integrated with and help further develop the respective educational setups[4-6]. Applicants are invited to propose any kind of research project they would like to get off the ground. Projects may be on any subject, ranging from epidemiology to biology or ethics. They may entail sophisticated experimental work or be primarily literature-based research projects that the WPA will be happy to share with the psychiatric community at large[7,8].

The proposed projects should ideally be in line with the current WPA Action Plan[9] and be coordinated in close collaboration with any or several of WPA Scientific Sections. Whenever feasible, the WPA encourages its Collaborating Centers to lend support to an ESPRI proposal. Intersectional efforts and the involvement of early career psychiatrists are highly encouraged. While we welcome an active role by researchers from non-LMICs in the proposed projects, we request that principal investigators on an ESPRI application be mainly based at an LMIC institution.

At this point, the WPA has set aside a sum of US $15,000 to be awarded to three projects annually, with the first projects selected by the end of 2019. The Executive Committee is cognizant of the fact that an initial sum of $5,000 may not be sufficient to implement a large-scale or long-term project and, hence, will work towards securing more funding in the future. However, the underlying idea of ESPRI is not to provide comprehensive funding, but rather to seed money to jumpstart a pilot project or proof-of-concept study.

The ESPRI seed funds are meant to be matched by funds the applicants have been able to secure through their respective institution, national and/or international funding organizations, governmental agencies, non-governmental organizations, and/or industry. These matching funds do not necessarily have to be cash, but may also be in-kind services like staff, space or logistical support that is equivalent to at least US $5,000.

The idea of accepting in-kind matching funds in lieu of cash support was developed in discussions with psychiatrists from Africa at the WPA Regional Congress taking place in Addis Ababa, Ethiopia in November 2018, taking into consideration the scarce financial resources in LMICs. Also, securing matching in-kind funds will require activating the aforementioned stakeholder networks and will thus be in and by itself an added value for the advancement of mental health infrastructures in the respective country or region.

As the WPA strives to minimize the logistical burden for applicants, we have introduced a straightforward application procedure. Applicants for an ESPRI award are asked to provide a one-page proposal outlining their project idea, a two-page curriculum vitae of each principal investigator (for a total of up to five), proof of matching funds, an endorsement by the Chair of at least one WPA Scientific Section, and an approval of a local research ethics committee, if applicable.

Until a page for ESPRI is added to the WPA website, the application package should be submitted via e-mail to the WPA Secretariat. The project should be completed within three years starting from the release of the funds. Yearly reports must be submitted outlining the progress of the study and the extent of funding being used. Publications based on the research results should acknowledge the funding provided by the WPA.

Proposals will be evaluated by a review committee including up to ten members drawn from WPA Scientific Sections. Applicants whose proposals are not selected for funding will be encouraged to resubmit a revised proposal if recommended by the committee.

The WPA Executive Committee looks forward to receiving a good number of high-quality proposals showcasing the innovative potential of psychiatrists and mental health experts in LMICs. We truly believe that research in LMICs and on LMIC-related topics should be initiated and carried out by researchers with a deep knowledge of the respective country or region or who are based in the region.

WPA's new signature program ESPRI is geared toward these researchers. It is meant to minimize, if not overcome, initial infrastructural, logistical or financial barriers. We are also hopeful that ESPRI will draw the attention of private or corporate donors, interested in supporting state-of-the-art global mental health research beyond the traditional and well-funded research institutions in high-income countries.

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The WPA website: newer user-friendly functions

The WPA website (www.wpanet.org) has been re-designed with several new functions and has gone live since May 2019. The website has now a number of features that make it a tool which is useful and user friendly. Several of these innovations are highlighted below.

A first new feature is that the website is able to tap into and take advantage of ongoing developments on a regular basis. So, the system is constantly being updated with the latest technological improvements. We use a sort of "pick and mix" approach which enables us to add the capabilities most useful to our visitors and to forego the ones that are not. For example, we have added a robust search system and the capability to translate into multiple languages. The site uses a simple, intuitive navigation system that allows users to find the content they need through a variety of different pathways[1-3].

In terms of data (according to Google Analytics), we have approximately 150 visitors to our site per day. The majority of these visitors are from the US. The top five countries using our site are US, Brazil, India, UK and Australia. Of the people visiting our site, approximately 85% are new visitors and 15% are return visitors. Users are going through 4-5 pages of our website per visit.

Visits peak considerably when something is sent out by the WPA Secretariat. We also saw a huge spike in visits (unsurprisingly) during the World Congress of Psychiatry held in Lisbon in August 2019, with more than 1,500 visits across the three full days of the Congress.

When on our site, approximately 10% of visitors use the search button to find what they want. The rest use the navigation. This is a good sign, as it means that people are finding what they need using the navigation alone.

The majority of visitors to our site are seeking information on meetings, followed closely by publications (about half of those then moving to *World Psychiatry*). After that, visits are focused on Scientific Sections (mostly requests to join), News and finally, Education[4-10]. We have an average of 1-2 enquiries and requests to be added to our mailing list submitted via the website each day.

To improve the website further, we are working at the moment on several new features. We are close to launching all our application forms for meeting co-sponsorship and continuing medical education (CME) as online submissions. This will mean that users no longer need to download and compile forms by hand, then scan and send them to the WPA Secretariat with various attachments. Instead, they will be able to simply compile them electronically, upload any attachments and submit all in one session. Obviously, this will also have great benefits at the other end, as the WPA Secretariat will no longer have to manage everything manually.

We are also close to launching an online payment function, which will allow to make payments to the Secretariat directly via the website (for meetings fees, CME requests and, eventually, member subscriptions as well). We are building out our education pages to ensure that we have all our educational resources accessible via one central point. This is one of the biggest pieces of work going on behind the scenes and will be a really useful tool for our members and other stakeholders.

The new format of the website ensures that we have the most up-to-date information at our fingertips. It allows us to add news as it happens and to provide visitors with a more interactive experience. This is a new beginning, as we are working behind the scenes, adding more materials and targeting it more precisely, so that every user can find the information relevant to him/her, and introducing more and more automated processes.

We hope that our collaborative work will make the WPA website an instrument to usher in innovative changes in psychiatry and mental health.

Roy Abraham Kallivayalil
WPA Secretary General

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The WPA's prison health position statement and curriculum

A core aim of the WPA is to work globally, in accordance with the Declaration of Madrid[1], to safeguard the provision of mental health care and treatment for people who require them. This safeguarding is of particular importance to people from vulnerable or marginalized groups, and to those who encounter unethical or inequitable care[2,3].

People in prison are one such group. Their international number is estimated to be over 11 million, this figure having increased by 24% since 2000[4], and they are known to present with higher levels of physical and mental disorders than the general population, as well as exhibiting high suicide rates and increased mortality rates following custodial release[5].

Although the human rights of people in prison are meant to be safeguarded by a number of internationally agreed human rights instruments[6,7], they are subject to violations in numerous nation-states throughout the world. These violations, which can cause or exacerbate physical and mental disorders, may take many forms. They can include excessive time in detention before trial, insanitary or unhygienic prison conditions, overcrowding, physical and sexual assault, unchecked and uncontrolled violence, low-quality food, inadequate medical care, excessive solitary confinement, corporal punishment, and the use of the death penalty[8,9].

Given the perilous situation faced by many prisoners across the world, and the frequent failure of nation-states to correct human rights violations where they exist, the development of a WPA position statement and curriculum in this area is both timely and necessary. We worked with colleagues from across five of the world's continents to develop this position statement to guide practice in this area, along with a curriculum to facilitate the training of medical students, health care and prison staff[10].

The WPA strongly believes in the delivery of equitable and ethical health care in prisons and abhors the inhumane and degrading treatment that has regularly been described in this field. The following fundamental positions have therefore been adopted:

- The WPA expects that all governments are clear about the purpose of their prisons to ensure that all imprisonment is reasonable, proportionate, decent, and humane. Health should not deteriorate or ill-health be exacerbated as a consequence of the custodial environment or its regime.
- The WPA supports mental health professionals in their work in prisons – this applies particularly in the event of any untoward or inappropriate discrimination, or any prevention of the ability to practice ethically based medicine, or of the need to speak out about any significant shortcomings.
- The WPA expects that people in prison who are socially, physically and mentally disadvantaged should have access to rehabilitation services, enabling them to lead purposeful and economically viable lives free from further criminal activity on release.
- The WPA advocates that people in prison throughout the world should, at all times, have timely access to the same range, amount and standard of mental health care services that are available to people in the general community.
- The WPA regards the accurate assessment and treatment of ill-health among people in prison as obligatory, as is the promotion of health and wellbeing.
- The WPA recognizes the high levels of mental health, physical health, and substance misuse morbidity with which people in prison present. Given these high morbidity levels, reception health screening should be universally provided, and effective mental health assessment and treatment readily available.
- The WPA understands that health and justice roles have the potential to conflict, and health care providers and practitioners should ideally function independently of the criminal justice system and be supported through the country's health care system.
- The WPA holds the clear view that health care providers should never be involved in punishment, inhuman or degrading treatment, or torture.
- The WPA expects the Bill of Rights for Persons with Mental Illness, and the Bill of Rights for Children and Young People with Mental Illness, to apply equally to people in prison, in the same way as they apply to the general community.
- The WPA considers that, to enable prison health care systems to function optimally, processes should be in place to ensure the independent monitoring of prison and health standards, with a robust complaints system. The needs of vulnerable groups such as women, pregnant women, those with intellectual disability, and lesbian, gay, bisexual and transgender individuals must be recognized and met.

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Conceptual work to advance psychiatric and neuroscientific sophistication: a report by the WPA Section on Philosophy and Humanities in Psychiatry

During the last few decades, psychiatry has developed considerably, also owing to neuroscientific advances. These developments, however, have uncovered a multitude of complexities, reflected for example in current controversies over psychiatric classification[1]. The bar for conceptual sophistication by which psychiatry has to account for these complexities theoretically and clinically has consequently raised.

Physics has been in a similar situation. Its subsequent turn to conceptual tools resulted in opening up new explanations and horizons[2]. Equally so, psychiatry is now reconsidering its conceptual foundations, in partnership with neuroscience, with the aim of addressing its complexities. Oxford Philosophy, for example, has many faculty members working either in physics or in psychiatry and cognitive neuroscience.

This paper reports on progress in this regard, which has been the remit of the WPA Section on Philosophy and Humanities in Psychiatry. We highlight the international impetus behind the progress for both theoretical work and clinical practice.

The WPA Section on Philosophy and Humanities in Psychiatry is closely linked with the International Network for Philosophy and Psychiatry (INPP), comprising 43 national associations. Since 1994, the INPP has hosted 20 international conferences, of which most were endorsed by the WPA and the Section, held across five continents. The 20th International Conference was held in Hong Kong in 2018, and the 21st International Conference took place on October 22-24, 2019 in Warsaw, Poland.

For the past 25 years, a vast resource of scholarly articles has been generated in the peer-reviewed international journal *Philosophy, Psychiatry & Psychology*, published by Johns Hopkins University Press. Furthermore, since 2003, Oxford University Press has published more than 50 books in the series *International Perspectives in Philosophy and Psychiatry*. These include the *Oxford Textbook of Philosophy and Psychiatry*, a 73-chapter *Oxford Handbook of Philosophy and Psychiatry*, and the *Oxford Handbook of Philosophy and Psychoanalysis*. All these volumes are strongly international in scope, reflecting the rich traditions of thought and practice available to support the development of psychiatry from all over the world.

Members of the Section have contributed to these and other publishing initiatives both as editors and authors. Currently, the Section is supporting the production of the volume *International Perspectives in Values-based Practice: Case Studies and Commentaries*, forthcoming from Springer Nature.

From the vast number of international scholarly publications mentioned above, much may be gleaned regarding the specifics of both theoretical and practical progress afforded by partnership between empirical and conceptual work in psychiatry. Here we highlight two examples: one on diagnostic classification and another on a practical skills-based approach relevant not only to psychiatry but also to the rest of medicine.

A recent Forum in *World Psychiatry*[3], with an introductory paper and a set of commentaries, is a fine example of how empirical and conceptual work come together in diagnostic classification of psychopathology. From both clinical and philosophical backgrounds, the authors of the introductory paper represent a consortium working towards a Hierarchical Taxonomy of Psychopathology (HiTOP). Notwithstanding their emphasis on quantification, their paper accounts for much in terms of conceptual work. For example, they describe a hierarchy ranging from more general and broad to more specific and narrow concepts. They highlight furthermore the need to devise strategies "to parse similarities and differences", and a need for "coherence in conceptualizing the entire breadth of the subject matter" since "a piecemeal classification would have limited utility in portraying the entire picture".

The title of the paper explicitly declares its topic as conceptual. The commentaries, some of which are authored by members of our Section, clarify the premises, strengths and limitations of the paper. The pursuit of the commentaries is squarely that of conceptual work: clarification of the concepts and the reasoning applied, particularly where the complexity of the material makes clarity rather challenging, as is the case for classifying psychopathology.

The second example originates from rigorous conceptual work that drew on philosophical value theory to articulate values complexity in psychiatry[4]. This has led to the development of a new skills-based approach to working with complex and conflicting values in health care, called values-based practice (VBP). VBP is a partner to evidence-based practice: it links science with people[5]. Although developed originally in psychiatry, VBP is now being taken up in the rest of medicine: for example, the lead discipline in the Centre for Values-based Practice in Oxford is surgery. This means that psychiatry has been leading the way for the rest of medicine on how to deal practically with the emerging choices (and values driving those choices) opened up by scientific advances in medicine.

VBP is a partner not only to evidence-based practice but also to a whole range of other ways of working with values in medicine. Examples include such familiar disciplines as ethics, medical law, and health economics, but also emerging fields such as decision analysis. VBP adds to this growing toolkit of methods a particular and distinctive focus on the uniqueness of individual values. This is important particularly in psychiatry, being key to the recovery processes of generating connectedness, hope, identity, meaning and empowerment[6], and has been endorsed more

widely in medicine through developments in human rights legislation and medical law[7].

VBP is an exemplar of how partnerships between conceptual and empirical research have brought conceptual resources to support psychiatry and other disciplines in responding appropriately to the complexities of clinical practice. VBP originates from conceptual analysis, but similar partnerships are seen in the work of Section members who have drawn on various other philosophical traditions, including phenomenology, ethics, African and Asian philosophies.

Inclusive partnerships are for example reflected in the recent *Oxford Handbook of Phenomenological Psychopathology*[8] and in the *Oxford Handbook of Psychiatric Ethics*[9], a double volume to which 149 authors across the world contributed, encompassing, in addition to a large part of the standard canon of psychiatric ethics, ground breaking domains essential to engaging with the diversity of values brought about by scientific advances in international psychiatry.

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Early career psychiatrists – history, 2020 and beyond

The support of the WPA to early career psychiatrists started in 1999, when several fellows were invited to attend the World Congress of Psychiatry in Hamburg, establishing the first WPA Congress Fellows Network.

In 2003, the WPA Executive Committee created the Young Psychiatrists Council, targeting all trainees and early career psychiatrists registered in the national psychiatric associations. Later, in 2009, this was restructured as the WPA Early Career Psychiatrists Council, with one representative nominated for a term of three years by each WPA Member Society. Under the leadership of A. Fiorillo, the Council was divided into five geographic areas: Europe I, Europe II, Asia/Australia, Africa and the Middle East, and Americas[1,2].

As the Council was not renewed after its first triennium, for a while early career psychiatrists did not have a WPA official entity. In 2014, a group of early career psychiatrists proposed the creation of a WPA Early Career Psychiatrists Section to secure the continuity of support from the WPA.

In 2015, the WPA Early Career Psychiatrists Section was created, with the leadership of H. El Kholy and a board of six people from different regions of the world. In 2017, a new Section leadership was elected, expanding the board to eight people, representing different world regions: Western Europe, Eastern Europe, North Africa and the Middle East, South Africa, North America, South America, Asia, and Australia and New Zealand. Although the name of the Section is "Early Career Psychiatrists", the term is overarching, as it represents and supports both psychiatric trainees and early career psychiatrists (up to seven years after becoming specialists in psychiatry), and there is no age limit or financial cost to be a Section member.

At the beginning of this triennium, we shared our views as early career psychiatrists about the future of psychiatry[3]. Then, in collaboration with the International Federation of Medical Students Association (IFMSA), we conducted a survey targeting medical students across the world, examining the psychiatric curriculum during medical education[4], with the support of the WPA Secretary for Education[5].

We have also been conducting a World Psychotherapy Survey, aiming to further understand how psychotherapy is included in the psychiatry training in different countries across the world, and how much access trainees have to it. Besides, further to the work of the WPA Brain Drain Task Force[6], the Section has been conducting a follow-up of the Brain Drain study[7] in collaboration with the European Federation of Psychiatric Trainees (EFPT). We have approached psychiatric trainees and early career psychiatrists across the world, investigating their patterns of migration, as well as their reasons to stay or leave their country.

In fact, within the medical field, mobility is growing at different levels, from patients to health professionals, raising the need for cross-cultural training to meet global health competencies. Yet, although internships abroad are of interest to many, several colleagues face difficulties in having access to such opportunities overseas. Thus, the WPA Early Career Psychiatrists Section has proposed an Exchange Programme in the WPA remit. This will be an innovative project, since there is not currently a worldwide psychiatric exchange program, supporting the mobility across different continents of the world. These worldwide exchanges will enable participants to engage in clinical, research or teaching activities abroad, learning about a (very) different educational programme or a (very) different mental health system. This will allow early career psychiatrists to acquire intercultural competencies, gain-

ing awareness of different expressions of illnesses and available treatments. These new experiences will stimulate professional networking, and the establishment of new partnerships and collaborations.

Another unique opportunity to bring colleagues from all over the world together has been the 3rd World Congress of Early Career Psychiatrists, that the Section has organized together with the Tunisian Association *Jeunes Psy*. Prominent speakers have been discussing the future of psychiatry together with early career psychiatrists. This meeting has been an inspiring occasion, strengthening the global network of early career psychiatrists.

Supported by the WPA, our Section seeks to promote the professional development of early career psychiatrists worldwide, offering several opportunities to its peer members. First, early career psychiatrists play an active role in the organization of the World Congress of Psychiatry, where an Advisory Committee of Early Career Psychiatrists has been set up since the Berlin Congress in 2017. The World Congress has several innovative sessions for early career psychiatrists that promote further interaction through the use of technology (such as the WPA 3 Minutes Competition, and more recently the Digital Interactive Theatre). Furthermore, the WPA has financed travel fellowships, supporting the attendance of early career psychiatrists to the World Congress.

Remarkably, the WPA has allowed numerous early career psychiatrists to present at the World Congress of Psychiatry, and for some this has been the first time ever speaking at an international congress. In addition, several colleagues have given presentations at regional or thematic WPA meetings across the world. Many of our Section members are also members of other WPA Scientific Sections, fostering the development of intersectional collaborations[8,9].

We keep our members updated with these opportunities and engaged with our events, which are publicized through our social media accounts (Twitter and Facebook), our members mailing list, and the Section Newsletter, which also features articles written by our members and collaborators.

The size of the WPA Early Career Psychiatrists Section has noticeably increased, with hundreds of members from continents around the world. The exceptional value of the WPA is the unique opportunity to accommodate the diversity of psychiatry, geographically and culturally, in its theories and its practice. Notably, across the world, early career psychiatrists are proud to be integrated and supported under the common umbrella of the WPA. Joining forces with drive and starting early in the professional career makes psychiatry precious and hopeful for its future.

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